FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE EXTENDED RELEASE PELLETS

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CONTENTS

LIST OF ABBREVIATIONS

ER	Extended Release
IR	Immediate Release
%	Percentage
Hrs	Hours
Min	Minutes
ml	Milliliter
µg	Microgram
g	gram
g/cm^3	gram per centimeter cube
mg/ml	milligram per milliliter
µg/ml	microgram per milliliter
µm	micrometer
M	Molarity
N	Normality
mg	Milligram
nm	Nanometer
Conc.	Concentration
HPMC	Hydroxy Propyl methyl cellulose
Temp	Temperature
NMT	Not more than
NLT	Not less than
Wt	Weight
Std	Standard
No	Number
i.e.	That is
^0C	Degree Celsius
UV	Ultraviolet/visible spectrometer

IP	Indian Pharmacopoeia
USP	United States Pharmacopoeia
w/v	Weight by volume
w/w	Weight by weight
v/v	Volume by volume
eq	Equivalent
QS	Quantity sufficient
LOD	Loss on drying

1. INTRODUCTION

1.1. Drug delivery system

The treatment of acute diseases or chronic illness has been achieved by delivery of drugs to the patients for many years. These drug delivery systems include tablets, injectables, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body (Loyd et al., 2006).

Another role of the drug delivery systems is to allow the safe application of the drug. This includes that the drug on the formulation must be chemically, physically and microbiologically stable. Side-effects of the drug and drug interactions should be avoided or minimized by the use of suitable drug delivery systems. The delivery systems also need to improve the patient's compliance with the pharmacotherapy by the development of conventional applications (Lee and Robinson, 2000)**.** For example, one can improve patient compliance by developing an oral dosage form where previously only par-enteral application was possible. Finally, the delivery system needs to be reliable and its formulation needs to be technically feasible. This means the pharmaceutical quality of the delivery systems needs to be absurd, drug release from the system needs to be reproducible and the influence of the body on drug release should be minimized (for example, food effects after oral administration). Drug delivery system is broadly classified into two types they are (Saptarushi D & Mukul S, 2009).

A. Conventional drug delivery systems.

B. Modified drug delivery systems.

A. Conventional drug delivery system

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional drug delivery is effective, but some drugs are unstable or toxic and have narrow therapeutic window and solubility problems (Leon lachman et al., 1986). In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels. This continuous drug delivery can be achieved by the use of controlled drug delivery systems. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience. The main goal of modified drug delivery systems is to improve the effectiveness of drug therapies (Howard C et al., 2000).

Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentrations versus time curve reflecting primarily the rate of absorption and elimination, respectively (Aulton M.E, 2000). Because of the rapid rate of absorption and elimination from conventional dosage forms, drugs are usually administered more than once daily, with the frequency being dependent on biological half life ($t_{1/2}$) and duration of pharmacological effect. The time of dosing may also be effected by therapeutic index of a drug (Schwartz BJ, 2000).

Limitations of conventional drug delivery systems

- In conventional oral dosage forms, there is little or no control over the release of the drug and effective concentration at the target site can be achieved by intermittent administration of glossy excessive doses.

- The dosing pattern in conventional dosage forms results in constantly changing, unpredictable and often sub-therapeutic plasma concentrations, leading to marked side effects in some cases.
- The rate and extent of absorption of drug from conventional formulations may vary greatly, depending on the factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the Gastrointestinal tract, Gastrointestinal motility and so on.
- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur (Peter ridgeway et al., 2001).

B. Modified Drug Delivery System

Dosage forms can be designed to modify the release of the drug over a given time after the administration or for a prolonged period of time or to a specific target in the body. Modifications in drug release are often desirable to increase the stability, safety and efficacy of the drug, to improve the therapeutic outcome of the drug treatment and to increase patient compliance and convenience of administration (William Andrew, Wise and Donald L, 2000).

Classification

Modified Release dosage form may be classified as

A. Delayed Release
B. Extended Release
    i. Sustained Release
    ii. Controlled Release

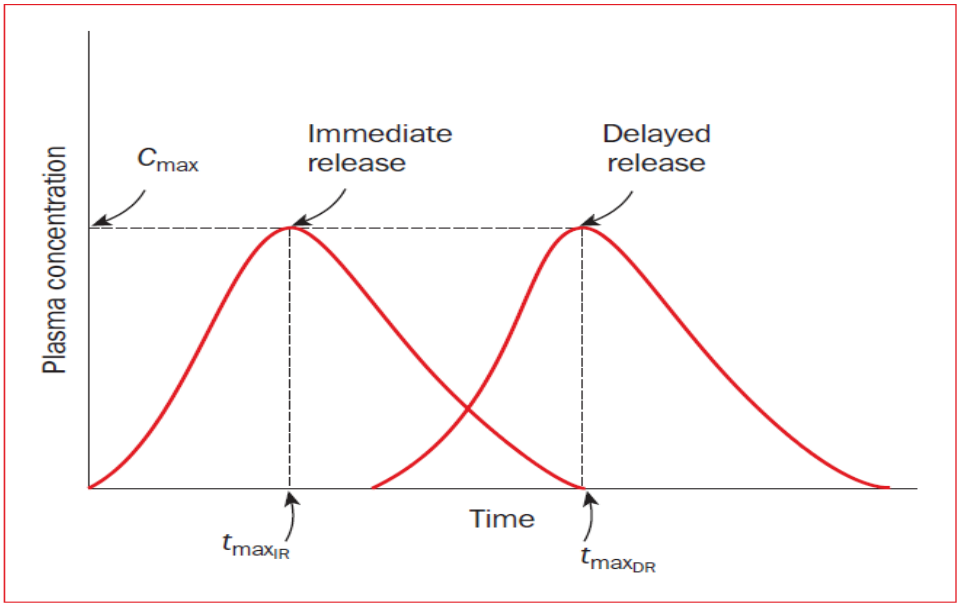
A. Delayed Release

A Delayed Release dosage form is designed to release the drug at a time other than promptly after administration. Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location.

Delayed Release oral dosage forms can control where the drug is released, e.g. when the dosage form reaches the small intestine (enteric-coated dosage forms) or the drug after a predetermined time in a predetermined location, i.e. they do not release the drug immediately after ingestion, for example enteric-coated tablets, pulsatile-release capsules. The oral route of drug delivery is typically considered the preferred and most patient-convenience means of drug administration. The release of drug from an oral dosage form may be intentionally delayed until it reaches the intestine (Brahmankar D M & Jaiswal S B, 1995).

The correct selection and balance of excipients and processes in solid dosage formulations are designed either for improving the micrometric or macro metric properties of materials during manufacture and/or for providing a desired drug delivery system. The mostly commonly used pharmaceutical delayed release solid oral dosage forms today include tablets, capsules, granules and pellets.

Figure 1: Delayed dosage form compared to an immediate-release dosage form



$tmax_{IR}$ is the time for maximum plasma concentration of the drug released from an immediate-release dosage form and $tmax_{DR}$ is the time for maximum plasma concentration of the drug released from a delayed-release dosage form (Chein Y.W, 1992).

Significance of delayed release systems

The design of such system involves release of drugs only at a specific site in the gastrointestinal tract. The drugs contained in such a system are those that are:

- Destroyed in the stomach by enzymes
- Known to cause gastric distress
- Absorbed from a specific intestinal site
- Meant to exert local effect at a specific gastro-intestinal site.

B. Extended release drug delivery system

Extended release system was introduced in the pharmaceutical market in the early 1950s by Smith Kline and French made an orally administered formulation of Dextroamphetamine sulphate by incorporating the drug pellets coated with wax.

Extended release dosage forms release drug slowly, so that plasma concentrations are maintained at a therapeutic level prolonged period of time (usually 12hrs) extended drug action at a pre-determined rate by maintaining a relative

constant, effect drug level in the body with concomitant minimization of undesirable side effects that are associated with a saw tooth kinetic pattern of conventional release (Remington, 2002).

The terms sustained release, time release, prolong release or extended release are used to identify drug delivery systems that are designed to achieve a prolonged therapeutic blood or tissue levels of the drug by continuous release of the extended period of time after administration of a single dose (Mankar et al., 1999).

Extended release tablets and capsules are commonly taken only once or twice daily. Typically extended release products provide an immediate release of drug which promptly products the desire therapeutic effect which then is followed by gradual and continual release of additional amounts of drug to maintain this effect over a pre-determined period of time. The sustained plasma drug levels provide by extended release drug products often eliminate the need for night dosing, which provides benefit to the patient.

Reasons for developing extended release drug delivery system

Immediate release of the active ingredient with resulting fast absorption rate may not always be desirable. If the drug has narrow therapeutic index, fast and complete absorption may result in plasma concentration that corresponds to toxic levels.

Advantages

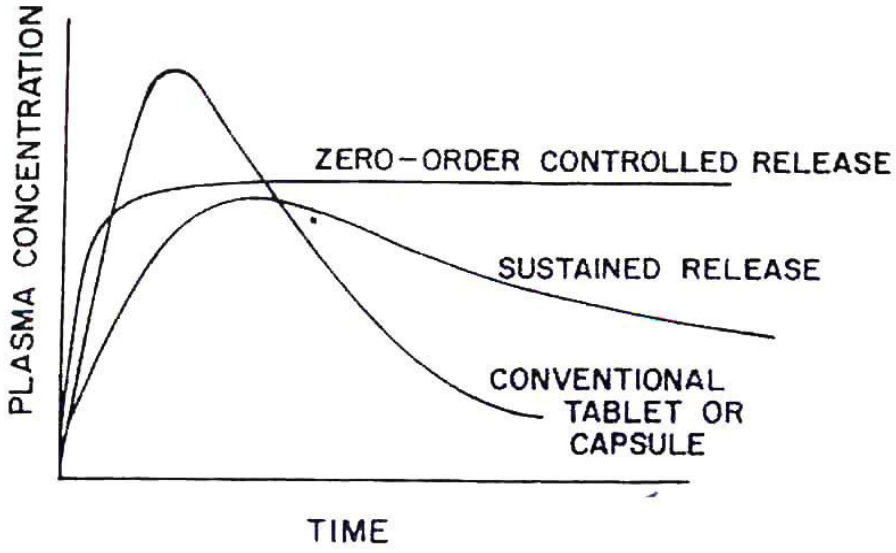
- Improved patient compliance
- Less frequent dosing (by reducing number of doses)

- Reduced patient care time
- Decreased local and systemic side effects
- Reduced Gastrointestinal irritation and other dose related side effects
- Improved efficiency in the treatment
- Optimized therapy
- More uniform blood concentration
- Reduction in fluctuation in drug level and hence uniform pharmacological response.
- Cure or control of condition more promptly
- Reduction in the incidence and severity of untoward systemic side effects related to high peak plasma drug concentrations
- Maintenance of the therapeutic action of a drug during overnight no dose period
  e.g.: Overnight management of pain in terminally ill patient's permits improved sleep.
- Employ less total drug.
- Minimum drug accumulation on chronic dosing

Disadvantages

- They are costly
- Dose dumping
- Increased variability among dosage units.

Figure 2: Plasma drug concentration profiles for conventional tablet or capsule formulation and extended release (sustained and controlled) formulation.



A. Sustained release dosage forms

Sustained release technologies can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and number of doses required. Furthermore, the possibility of repeating successful drugs, coupled with the increasing expense in bringing new drug entities to market, has been instrumental in generating interest in sustained-release dosage forms.

The sustained release dosage form is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug". Once the maximum level is reached, the amount of drug in the body decreases slowly so it will take longer to drop below the therapeutic range.

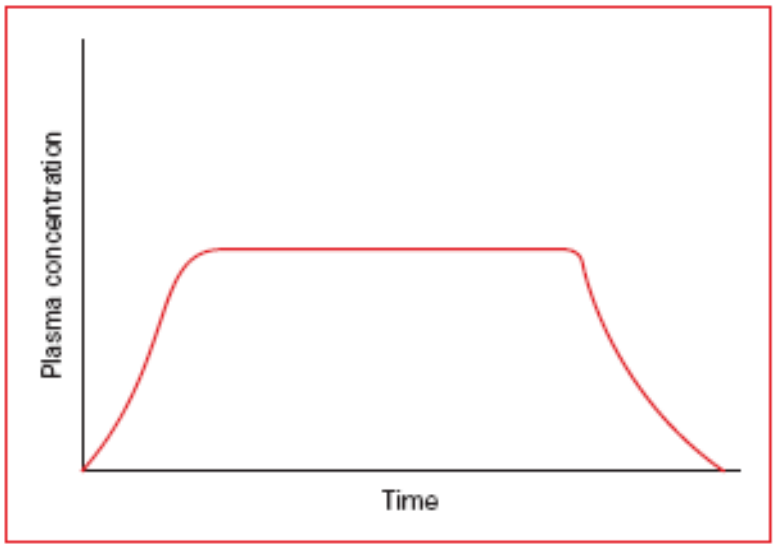
The terms sustain or controlled drug release incorporates the element of prolongation of duration of drug action as well as the drug predictability and reproducibility in drug release kinetics. Polymeric sustained drug delivery systems

offer numerous advantages when compared with conventional dosage forms, including improved efficacy, reduced toxicity, and improved patient compliance.

B. Controlled drug delivery

Controlled drug delivery of drug s delivery of drug at a rate or at a location determined by needs of body or disease state over a specified period of time (Chein Y. W, 1989).

Figure 3: Dissolution profile of controlled release dosage form.



The release system is formulated to dissolve slowly and release a drug over time. The main advantage of controlled release tablets and capsules are that they can often less frequently than instate release formulations (Brahmankar D M, 1995).

There are certain conditions for the formation of controlled release formulation:

1. If the active compound has a long-life (over 6hrs), it is sustained on its own.
2. If the active compound has a short long-life it would require a large amount to maintain a prolonged effective dose.

3. In case of broad therapeutic window, it is necessary to avoid toxicity, otherwise, the risk is unwarranted and another mode of administration would be recommended.

The basic goal of controlled drug delivery system is to achieve a steady blood or tissue level of a drug at a specific site, which will be therapeutically effective and non-toxic. The enteric coated pellets and tablets deliver the drug almost at a pre-determined rate locally for a specified period of time at a specific site by reducing adverse effect. When compare with the other conventional dosage forms like tablets or capsules the maximum administration dose is very fewer amounts after maximum administration of dose it will cause toxicity. Such type of active pharmaceutical ingredients is administered by extended release preparations. The bioavailability of drugs is more when compare with the tablets surface area of the pellets is more. In case of tablet coating uniform coating is not occurred dose dumping will occur, in case pellets if any pellet is not coated well the effect will be minimized by the other pellets for that only pelletization is more effective preparation.

Biopharmaceutical drug classification

Class I: High solubility- High permeability

Class II: Low solubility- High permeability

Class III: High solubility- Low permeability

Class IV: Low solubility- High permeability

The above classification is mainly by taking the solubility and permeability characters of the drug into the consideration. This is the most acceptable classification of the drugs in the pharmaceutical industry. The present drug has high solubility and permeability characteristics. Solubility and permeability play an influential role in the

performance or conventional products (Lee et al., 2001). Their role is even greater in extended release systems. The present drug i.e Metoprolol succinate belongs to the class I (Lordi N. G. 1991 & Robinson R & Lee V. H 1995).

The below factors also play a key role in extended release systems (Kinam P et al., 2009).

1) Aqueous solubility and Pka
2) Partial ion co-efficient
3) Drug stability
4) Molecular size
5) Rate of diffusion
6) Protein binding.

Capsules

Capsules are solid dosage forms in which the drug or a mixture of drugs are enclosed in hard or soft gelatin capsules. These shells are made up of gelatin and are available in various sizes, shapes and capacity.

Types of capsules

1) Hard gelatin capsules
2) Soft gelatin capsules
3) Sustained release capsules
4) Enteric capsules

Capsules evaluation tests and standards

1. **Description**

   The color, size and shape of the capsules are examined visually and they are reported. The color, size and shape of the capsule should be acceptable by the patient and should be conveniently taken up by the patient i.e. the capsule dosage form should be palatable.

2. **Content of active ingredients (Assay)**

   The assay is done to check the drug content in the formulation and to indentify whether it complies with the specified limits that are specified.

Limit:- 90 to 110% of label claim or as per in house limit.

3. Uniformity of weight

This evaluation test is done to know whether all the formulations consists of the same amount of drug (Park, 2009).

Table 1: Standard values for uniformity weight of capsules

Average weight of capsules	Percentage deviations
Less than 300 mg	10%
300 mg or more	7.5%

4. Disintegration test

The disintegration test is done to know the time needed for the disintegration of the capsule shells and to release its components into the buffer solution.

Hard gelatin capsules: Disintegration time shall not be more than 30 min.

Soft gelatin capsules: Disintegration time shall not be more than 60 min.

Enteric capsules: Acidic media- shall not disintegrate in 2 hrs

Basic media- shall disintegrate within 30 min.

5. Standard length for hard gelatin capsules in "mm"

Table 2: Standard length of hard gelatin capsules

Size	Cap	Body
0	10.68-11.68	18.22-19.22
1	9.51-10.51	16.22-17.2
2	8.67-9.67	14.84-15.84
3	7.73-8.73	12.98-13.98
4	6.97-7.97	11.84-12.84

6. **Microbial limits**

   This is checked to identify any microbial content in the capsule shell. The standard limit for the microbial content is NMT 1000 ppm/gm of capsules shell.

7. **Loss on drying**

   The loss on drying is measured to know the moisture content in the mixture and it is also used to know the weight of the sample without moisture. Between 12.5% and 16% detrained on 0.3 gm of shall by drying in oven at 105°C for 4 hrs at constant weight.

Reason for selecting capsules

The Metoprolol succinate is available in tablet form, the research is going on to formulate an efficient capsule dosing form due to its advantages over the tablet dosage form. It should be kept in mind that pharmaceutical compositions formulated in tablets are subject to variations in their physicochemical properties such as hardness, disintegration time and dissolution time and also on dissolution rate due to the compression process involved in their production. Such variations are of course undesirable in extended release Metoprolol succinate capsules, since the prediction of the dissolution rate is an extremely important factor for the efficiency of the formulation. Finally extended release multi-particulate formulations of Metoprolol Succinate provide a better drug release at the gastro-intestinal tract compared with single tablet formulations.

Pellets
Definition

pellets can be defined as small, free flowing, spherical or semi-spherical solid units, typically from about 0.5mm to 1.5mm, and intended usually for oral administration, manufactured by the agglomerates of fine powders or granules of bulk drugs and excipients using appropriate equipment (Gennrao R A, 2009). Pellets can be prepared by many methods, the compaction and drug layering being the most widely used today (Cleland J.L & Langer R, 1997).

Regardless of which manufacturing process is used, pellets have to meet the following requirements.

1. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.
2. The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 mm and 1000 mm.
3. The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

Significance of pellets

Pellets may have varied applications in varied industries. It just requires an innovative bend to use it to derive maximum profitability. The smooth surface and the uniform size of pellets allow uniform coating not only for each pellet but also from batch to batch.

Highlighted below are some of the few instances where smooth surfaced uniform pellets are successfully used:

1. Improved appearance of the products. Coating of pellets can be done with different drugs to enable a controlled release rate.

2. In case of immediate release products larger surface area of pellets enables better distribution.
3. Chemically incompatible products can be formed into pellets and delivered in a single dose by encapsulating them.
4. In the chemical industries it is used to avoid powder dusting.
5. Varied applications are possible in the pellet form. Example: sustained release, controlled release, immediate release and etc..
6. Pellets ensure improved flow properties, and flexibility in formulation development and manufacture.
7. The coating material may be colored with a dye material so that the beads of different coating thickness will be darker in color and distinguishable from those having fewer coats.
8. The beads or granules of different thickness of coatings are blended in the desired proportions to give the desired effect.
9. The thickness of the coat on the pellets dictates the rate at which drug or contents are released from the coated particles. A smooth surface of the pellets and uniform coating thickness for each pellet.
10. By selecting the proper formulation, processing conditions and processing equipment it is possible to attain smooth surfaced and uniform pellets.

Advantages of pelletization

1. Improved appearance of the product and the core is pharmaceutically elegant.
2. Pelletization offers flexibility in dosage form design and development.
3. Pellets are less susceptible to dose dumping.
4. It reduces localized concentration of irritative drugs.
5. It improves safety and efficacy of a drug.
6. Pellets offer reduced variation in gastric emptying rate and transit time.
7. Pellets disperse freely in G.I.T and invariably maximize drug absorption and also reduce peak plasma fluctuation.
8. Pellets ensure improved flow properties in formulation development.
9. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules.
10. In the chemical industries it is used to avoid powder dusting.
11. In case of immediate release products larger surface area of pellets enables better distribution.

12. Chemically incompatible products can be formed into pellets and delivered in a single dose by encapsulating them.
13. Varied applications are possible in the pellet form. Example: sustained release.
14. The thickness of the coat on the pellets dictates the rate at which the drug or contents are released from the coated particles. A smooth surface of the pellets and uniform coating thickness for each pellet provides a good release.
15. The coating material may be colored with a dye material so that the beads of different coating thickness will be darker in color and distinguishable from those having fewer coats.

The most important reason for the wide acceptance of multiple unit products is the rapid increase in popularity of oral controlled release dosage forms, Controlled release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the GIT or to sustain the action of drugs over an extended period of time. With pellets, the above mentioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function or through the formulation of matrix pellets to provide the desired effect. The advantage of multiple unit products as a controlled release dosage form is believed to be their behavior in-vivo because of their advantageous dispersion pattern in the GIT and their special size characteristics (Vyas S.P & Khar R K, 2002).

Product characteristics

- Dust free
- Round pellet
- Good flow behavior
- Easy to dose
- Compact structure
- Low hygroscopicity
- High bulk density
- Dense, uniform surface
- Narrow grain size distribution
- Low abrasion

- High active ingredient content is possible
- Optimum starting shape for subsequent coating

Theory of pellet formation

In order to judiciously select and optimize any pelletization or granulation process, it is important to understand the fundamental mechanisms of granulate formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. As the conventional granulation, the most thoroughly studied, most classified pelletization process, which involves a rotating drum, a pan or a disc, has been divided into three consecutive regions: nucleation, transition and ball growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer (Chein Y.W, 1989).

Methods of preparing pellets

Compaction and drug layering are the most widely used pelletization techniques in the pharmaceutical industry. Of the compaction techniques, extrusion and spheronisation is the most popular method and in drug layering the wurster process is most widely used. Recently melt pelletization has been used frequently in making compaction pellets using a different type of equipment, for example: a high-shear mixer. Other pelletization methods such as globulation, balling and compression are also used in development of pharmaceutical pellets but in a limited scale.

Figure 4: Layered pellet internal characteristics and layered pellet

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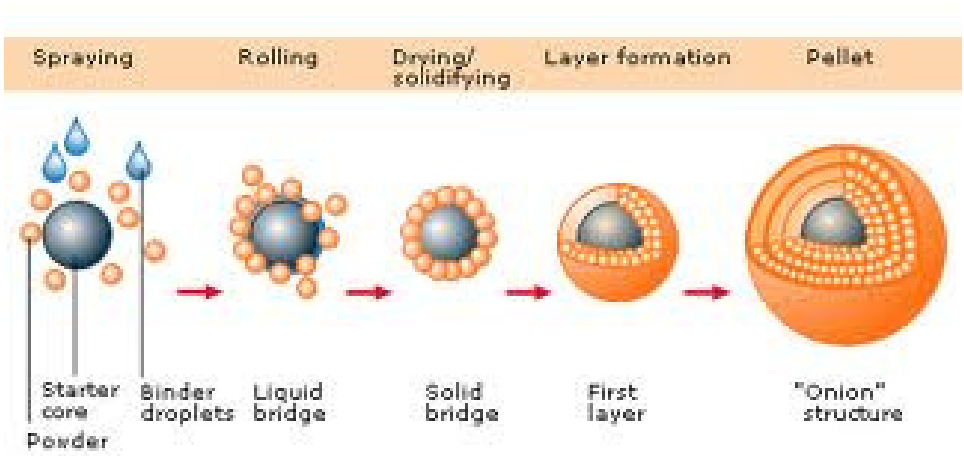
A. Powder layering

In this technique the dry powders of the drug an its excipients are mixed thoroughly and they are deposited as the successive layers over the inert core. the binding liquids are used for the deposition of the dry powder layers. This process takes place mostly in a specialized equipment known as the spheroniser. The container should be made of solid walls. There should be no perforations in the container walls. The walls should be of smooth in texture so that the powder should not be attached to the walls of the container.

Figure 5: Powder layering

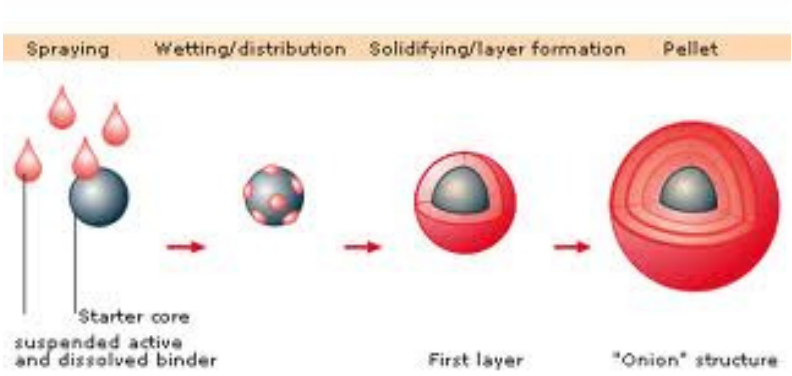


B. Solution/suspension layering

In this technique the drug along with its excipients are weighed accurately and are mixed in a solution to form a uniform suspension. Then this mixture is coated on the inert core materials. The coating should be done in such a way that the inert cores are uniformly coated with the drug suspension. this process involves mainly the wurster process. These involves the equipments such as coating pans, centrifugal granulators and fluidized bed processors. mostly the inert core material used is the

sugar spheres. The efficiency of the process and the quality of the pellets produced are related to the type of equipment used and the conditions or parameters that are used during the coating process.

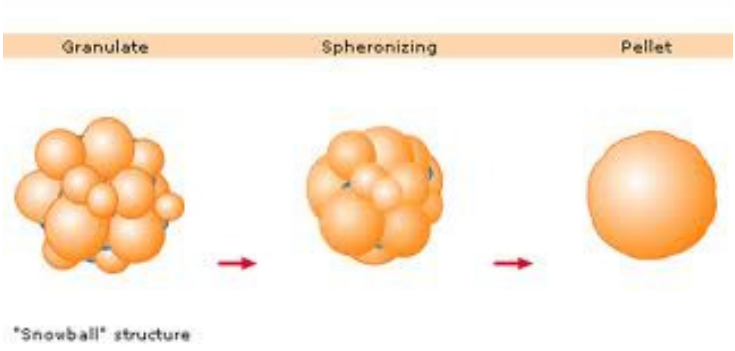
Figure 6: solution or suspension layering

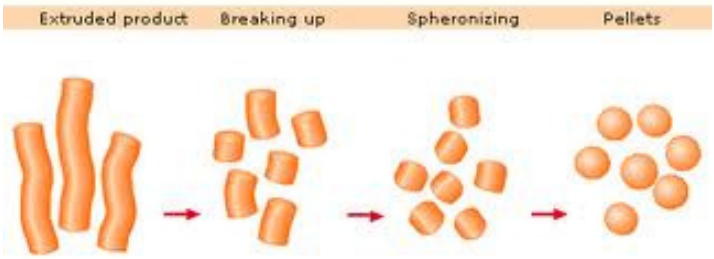


C. Pelletization by extrusion and spheronisation

In this process the drug along with its excipients are taken and mixed together to form mass. Then these are converted to form the extrudes through the process extrusion and then these are converted into small beads like structures through a process known as spheronisation. Nowadays equipments are available by which both the extrusion and spheronisation are done simultaneously in a single equipment. Through his process beads as fine as 0.6 mm can be obtained (Gibson, 2009).

Figure 7: Pelletization by spheronisation and extrusion





D. Other methods

Other pelletization methods such as globulation, cryo-pelletization, balling and compression are also used, although these are used for a limited scale of preparation of pharmaceutical pellets in the pharmaceutical industry.

Globulation

This involves both the spray drying and spray congealing processes. In this process the drug is mixed with its excipients and is converted into a uniform suspension by using a suitable vehicle. Then this solution is taken into special equipment where the drug suspension is sprayed in the form of fine particles and hot

air is blown from the bottom by which the fine droplets are condensed and dried and forms small particles known as pellets.

Spray congealing

In this process the drug is mixed with its excipients and is converted into a uniform suspension by using a suitable vehicle. Then this solution is taken into special equipment where the drug suspension is sprayed in the form of fine particles and hot air is blown from the bottom by which the fine droplets are condensed and dried and forms small particles known as pellets. Both immediate and controlled release pellets can be prepared in this process by taking the ingredients of different physicochemical and altering the other formulation variables.

Cryo - pelletization

In this process the drug is mixed with the required excipients and if formed into a suspension or solution form. Then this solution form or suspension form is spayed and is converted into spherical particles and allowed to pass through the liquid nitrogen medium. Then the spherical particles are condensed to form into solid particles. The liquid nitrogen is used as the fixing medium. The shape of the spherical particles depends on the distance travelled by the suspension before coming in contact with the liquid nitrogen.

Compression

This is the simple process in developing the pellets. this process involves the mixing of the drug and its excipients and the they are compressed to form the

condensed products. This is one of the compaction technique. The process variables which control the quality of tablets is similar to the preparation of pellets by this process.

Balling

In this process, the drug along with its excipients are taken and they are mixed thoroughly. Then they are placed in the pans or discs with continuous circular motion. When the drug mixture along with its excipients are placed in these equipments then the a suitable liquid agent is added. Then the mixture is mixed thoroughly. In this process the mixture combines with the liquid agent and forms small spherical structures.

Excipients for pellets

Formulation aids or excipients are added to pharmaceutical dosage forms mainly to produce satisfactory delivery of the drug to the intended site, to impart favorable characteristic to the dosage form and to facilitate the manufacture of the product. Since pellets are intended to be administered orally. The excipients used in the pellet dosage forms are typically the same as those used in tablet or capsule formulations. The different types of the excipients, disintegrants, surfactants, pH adjusters, separating agents, spheronization enhancers, glidants and release modifiers etc.. that are used in the development of the pellets are given in the following table.

Table 3: Examples of commonly used excipients.

Filler	MCC, starch, sucrose, lactose, mannitol
Binder	Gelatin, HPC, HPMC, MC, PVP, sucrose, starch,
Lubricant	Calcium stearate, glycerin, PEG, Magnesium stearate
Separating agent	Kaolin, talc, silicon dioxide

Disintegrant	Alginates, cross carmellose sodium, MCC, avicel
pH adjuster	Citrate, phosphate, meglumine.
Surfactant	Polysorbate, SLS.
Spheronization enhancer	MCC, sodium CMC
Glidant	Talc, starch, Magnesium stearate.
Release modifier	Ethyl cellulose, carnauba wax, shellac.

Sugar spheres (Non pareil seeds, neutral pellets)

"Sugar spheres contain not more than 92% of sugar, calculated on dry basis. The remainder consists of maize starch." defined according to European pharmacopoeia. Possibility to analyze the sugar spheres according to the Ph. Eur., USP/NF and JP. Produced accordance with the GMP. The sugar spheres are spherical in structure these are in the manufacture of the pellets. These can be involved in the development of the immediate release dosage forms or extended release dosage forms or delayed release dosage forms. The drug suspension is prepared and is coated on the sugar spheres to develop the immediate release dosage forms. The polymer coating can be used to retard or extend the release of the drug from the pellets, this is used in extended release dosage forms. In the delayed release dosage forms the pellets are coated with an enteric coating to protect the acid labile drug.

Coating equipment

Most of the coating processes use one of the three general types of equipments.

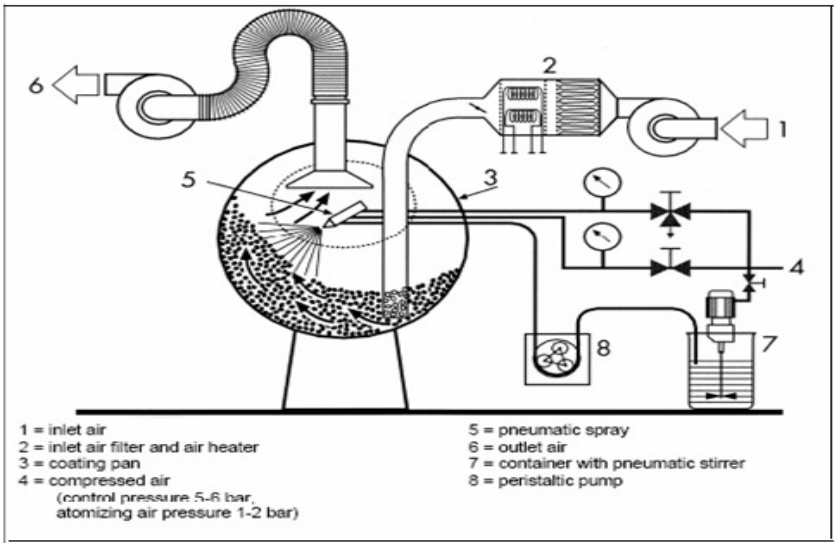
1. The standard pan.
2. The perforated pan.
3. The fluidized bed coater.

1. Conventional pan system

The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on its horizontal axis by a motor,

the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan. Coating solutions are applied by spraying the material on the bed surface.

Figure 8: conventional coating pan.



2. The perforated coating pan

Neocota is an automatic coating system for tablets and pellets. Neocota is a completely updated automatic coating system having a batch capacity of 500 gm to 1 kg. This model efficiently carries out the following operations: aqueous film coating of tablets/pellets; Non-aqueous organic solvent based film coating of tablets/pellets; and enteric film coating of tablets/pellets.

The basic system are has coating pan with perforations along its cylindrical portion. It is driven by a variable speed drive with a flame-proof motor. Supply of hot air and exhaust of drying air are arranged to facilitate the coating system through stainless steel plenums positioned on both sides of the perforated coating pan. The pan

is enclosed in a cylindrical airtight housing provided with a suitable door and front glass window. This housing of pan with drive is a stainless steel cabinet accommodating the gearbox, AC variable drive, power panel, hot air unit, exhaust unit and an air fitter. Liquid spray system is complete with stainless steel liquid storage vessel, variable flow-rate liquid dosing pump, automatic spray gun and inter-connecting flexible hoses.

3. The fluidized bed coater

The fluid fed technology offers a very efficient coating technique. The major advantage of the Fluid Bed Systems is that it is as per GMP standards and a closed system. The second advantage of the Fluid Bed Systems is that not only coating but granulation and pellet formation is also possible in the same machine.

Fluidized bed coating is a process that takes place inside a fluidized bed where by a coat is introduced to cover the intended object in order to protect it or modify its behavior. Particulate coating is a form of fluidized bed coating involving the coating of solid particles inside the bed. In this process, a layer is deposited onto the surface of fluidized solid particles by spraying with a solution of the coating material. The fluidizing gas is also use to dry the deposited solution to form a coat on the surface of the particle. There is considerable diversity in methods of using fluidized bed technology. For e.g. liquids can be applied to fluidized particles in a variety of ways, including top, bottom and tangential spraying. For a given product, each method can offer markedly different finished product characteristics. Fluidized beds are used for coating because of their high energy and mass transfer. Fluidized beds for film coating can be divided into three groups

1. Top-spray.
2. Bottom-spray equipment.
3. Tangential-spray.

1. Top spray

The expansion chamber is lengthened to allow powder to remain fluidized longer and to move with a higher velocity, so that agglomeration is minimized. The expansion chamber is conically shaped to allow uniform deceleration of air stream. The filter housing is larger and designed to shake the fines back into the bed interrupting fluidization; this reduces agglomeration tendencies. The nozzle is positioned low in the expansion chamber so that coating material impinge on the fluidized particle a short distance from the nozzle; this reduces droplet spray drying and provides for longer subsequent drying from the nozzle; this reduces droplet spray drying and provides for longer subsequent dying of the coated particles. The top spray coater has been used to apply aqueous and organic solvent based film coatings, controlled release coatings.

2. Bottom spray coating (wurster process, 1953)

The wurster machine employs a cylindrical product container with a perforated plate. Inside the container is a second cylinder (coating partition) which is slightly raised above the perforated plate, centered in the plate below this partition is a spray nozzle used to dispense the coating solution. The perforated pate is designed with large holes in the area under the coating partition and smaller holes in the remainder of the plate, except for one ring of large holes at the perimeter. The design allows the substrate particles to be pneumatically transported upward through the

coating partition and downward outside this partition. Material passing through coating partition receives a layer of coating material, dries in the expansion chamber and falls back in a semi-fluidized state. Material circulates rapidly in this fashion and receives a layer of coating material, dries in the expansion chamber and falls back in a semi-fluidized state material circulated rapidly in this fashion and receives a layer of coating on each pass through the coating partition. The ring of large holes on the periphery of perforated plate prevents the accumulation of material at the container wall it has been used for coating small particles, pellets and tablets (wurster process, 1953).

Figure 9: Bottom spray coater

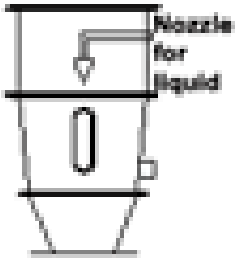
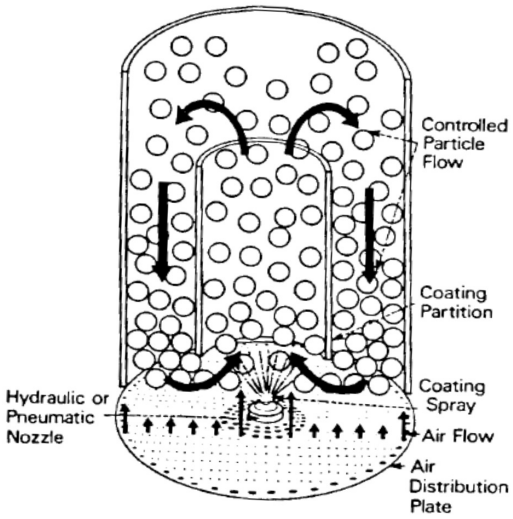


Table 4: Parameters used in bottom spray equipment

Inlet temperature	38-42°C
Product temperature	32-36°C
Exhaust temperature	32-38°C
Spray rate	8-12mg/min

Peristaltic pump	12-18 rpm

Figure 10: Fluid bed processor pictorial representation (wurster process).



3. Tangential spray coating (Rotating disk granulator)

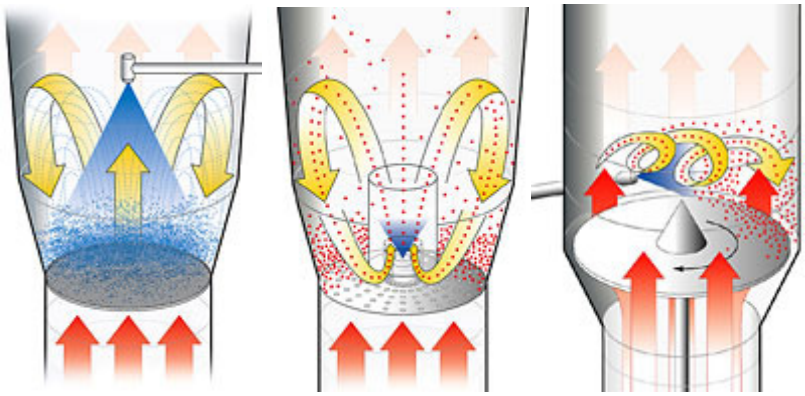
Granulation techniques utilizing centrifugal fluidizing drive have been studied only recently. These techniques have been extended to coating operations and combined with an expansion chamber to form the rotating disk granulator and coater fluid bed device. The basic design a rotating disk in the product container.

The disk can be moved up or down to create a variable slit opening between the outer perimeter of the disk and the sidewall of the container. Air is drawn into the product container through the slit under negative pressure. This fluidizes the material along the circumferential surface of the product container. At the same time the disk

rotates at varying speeds and moves the product by the centrifugal force to the outer portions where it is lifted by the fluidizing air steam into the expansion chamber. As the material decelerates, it descends to the center of the disk and repeats the same sequence. The fluidization pattern is often described as a spiraling helix or rope-like pattern around the inside of the rotor chamber.

Spray nozzles can be immersed in the bed of fluidized material and spray applied in tangential fashion with respect to the particle flow.

Figure 11: Various fluid bed coating techniques.



Top spray Bottom spray Tangential spray

2. REVIEW OF LITERATURE

Prasanth et al., (2011) in this study also the formulations are made by varying the concentrations of the polymers Hydroxy propyl methyl cellulose and ethyl cellulose. In this the drug and polymer ratio used were 1:2. The polymers were also used in varying concentrations to each other, the formulations were made by increasing each polymer concentration alternately. In the formulation with more concentration of ethyl cellulose showed more extended drug release from the formulation.

Anand et al., (2011) this study was done to develop and optimize extended release formulation of Tamsulosin hydrochloride using the combinations of polymers lke ethyl cellulose and eudragit as coating material. In the preparation of the primary coating HPMC E-5 was used and SLS was used as the wetting agent. To optimize the formulation various evaluation tests were conducted like the uniformity of size, assay and the in-vitro dissolution tests. The optimized formulation was obtained by using eudragit at 9% and ethyl cellulose at 25% of the drug content.

Rama Rao Nadendla et al., (2011) the purpose of the present study was to design, characterize and *in vitro* evaluation of sustained release pellets of metoprolol succinate to reduce the dosing frequency employing pan coating technology. Initially metoprolol pellets were prepared by solution layering technology over non-pareil seeds employing pan coating technology. Later, to sustain the release of drug over a period 20 hrs, secondary coating was given over the drug layered pellets using ethyl cellulose/ ethyl cellulose-hydroxy propyl cellulose were used to prepare different formulations. The prepared pellets were further evaluated for surface texture, flow

properties and *in vitro* dissolution studies. Formulation F6 showed promising results by sustaining the drug release up to 20 hrs. The *in vitro* dissolution studies revealed that the release rate is inversely proportional to percent of coating thickness. The mechanism of drug release follows Higuchi diffusion model.

N. N. Rajendran et al., (2011) the present study was aimed to develop an extended release tablet of Metoprolol Succinate for the treatment of hypertension. Four extended release formulations F1-F4 were developed using varying proportions of Hydroxyl propyl methyl cellulose K100M, Sodium carboxy methyl cellulose and Eudragit L30 D55 by wet granulation. Five extended release formulations F5-F9 containing HPMC K100M and HPMC 5cps in varying concentration were developed by direct compression. The physico-chemical and *in-vitro* release characteristics of all the formulations were investigated and compared. Two formulations, F7 and F8 have shown not more 25% drug release in 1st h, 20-40% drug release at 4th h, 40-60% drug release at 8th h and not less than 80% at 20th h and the release pattern conform with USP specification for 24 h extended release formulation. It can be conclusively stated that optimum concentration of HPMC K100M (58-65%) by direct compression method can yield an extended release of Metoprolol succinate for 24 hours.

Parmar *et al.*, (2011) the aim of the current study was to develop once-daily sustained-release matrix tablets of metoprolol succinate, Selective β1- blocker used in cardiovascular diseases. The tablets were prepared by the wet granulation method. Ethanolic solutions of ethylcellulose (EC), polyvinylpyrrolidone K30 were used as granulating agents along with hydrophilic matrix polymer hydroxypropyl methylcellulose (HPMC K100M). The results of dissolution studies indicated that batch AH3 (Drug-to-HPMC K100M, ethyl cellulose solution (4%W/V, as granulating

agent) could extend the drug release up to 24 hours. Batch AH3 showed highest f2 value 84.95 and MDT 8.9 hrs similar to that of reference product. The dissolution data were subjected to model fitting analysis and best fitted model was Higuchi model. All the formulations (except batch AH3) exhibited diffusion-dominated drug release. The mechanism of drug release from batch AH3 was diffusion coupled with erosion.

Ajay L. et al., (2010) this work aims at investigating different types and levels of hydrophilic matrixing agents, including sodium alginate (Alg), and Hydroxypropyl methyl cellulose K15M (HPMC K15M) in an attempt to formulate controlled-release matrix tablets containing 50 mg Metoprolol Succinate. The tablets were prepared by wet granulation. The Influence of three granulating fluid, viz acetone, isopropyl alcohol (IPA) & Dichloromethane (DCM) were also studied with a view to design & develop slow release formulation of Metoprolol succinate. Prior to compression, the prepared granules were evaluated for flow and compression characteristics. In vitro, newly formulated controlled-release tablets were compared with standard commercial tablets (Met®XL50). The excipients used in this study did not alter physicochemical properties of the drug, as tested by FTIR. The prepared matrix tablets showed good mechanical properties (hardness and friability). Hydroxypropyl methyl cellulose and Alginate-based tablet formulations showed high release retarding efficiency, and good reproducibility. FTIR study suggesting that HPMC K15M and Alginate are good candidates for preparing modified release tablet formulations Metoprolol succinate.

B. Yilmaz (2010) in this study, zero-, first-, second- and third-order derivative methods were developed for the determination of metoprolol in pharmaceutical preparations. In zero order spectrophotometry, absorbance values were measured at 276 nm in zero order spectra of solution of metoprolol in methanol in the range of

240-310 nm. In first derivative spectrophotometry, absorbance values were measured at 265, 278 and 285 nm. In second derivative spectrophotometry, absorbance values were measured at 276, 279, 287 and 282 nm. In third derivative spectrophotometry, absorbance values were measured at 275, 278 and 281 nm. Parameters such as linearity, precision, accuracy, specificity, stability, limit of detection and limit of quantization were studied according to the International Conference on Harmonization Guidelines. All the methods developed were successfully applied to two tablet formulation and the results were compared statistically with each other.

Gummudavelly et al., (2010) formulate and characterize extended release matrix tablets of metoprolol succinate using hydrophilic polymers like Hydroxy Propyl Methyl Cellulose (HPMC K100M), Hydroxy Propyl Cellulose (HPC), Ethyl Cellulose, Carbopol 934 and Megnesium Stearate, and these selected matrices were directly compressed into tablet. Release kinetics evaluated by using USP-22 (Paddle) dissolution apparatus. *In-vitro* release study showed that ERT10 for 25mg label claimed were well suited to extend release for 20 hours with zero order release.

Bhupendra et al., (2010) this study was conducted to develop once daily tablet of Nicorandil for the treatment of angina. In this study both the polymers HPMC (hydrophilic) and ethyl cellulose (hydrophobic) were used in different proportions to develop the extended release tablet. When the formulation was incorporated with HPMC and Ethyl cellulose in 1:2 ratio is showed the sustained drug release for about 22hrs and the drug release was found to be 91%.

Manna niranjan kumar et al, (2010) mucoadhesive microcapsules of metoprolol succinate ,a β1-adrenergic blocker and antihypertensive agent , have been

prepared from sodium alginate ,hydroxyl propyl methyl cellulose-K4M&E5LV,carbopol 934P, sodium CMC using 10% w/v calcium chloride solution by ionic gelation method. Drug : polymer ratio was 1:1 in all formulations and polymer mixtures employed were 1:1,2:1,3:1,4:1 of sodium alginate: polymer(hydroxyl propyl methyl cellulose-K4M&E5LV, carbopol 934P, sodium CMC).Calcium chloride was used for ionic gelatin and cross linking of sodium alginate molecules. Microcapsules were spherical in shape and of sizes between 585 microns to 845 microns . Carbopol 934P was found most effective in controlling drug release from microcapsules followed by hydroxyl propyl methyl cellulose K4M. Drug release from the best formulation from carbopol 934P follows Higuchi model while that from hydroxyl propyl methyl cellulose K4M follows anomalous transport.

Antesh K Jha et al., (2009) the objective of the present study was to develop sustained-release matrix tablets of metoprolol succinate, β1-selective adrenergic receptor blocking agent. The tablets were prepared by the wet granulation method. Ethanolic solutions of ethylcellulose (EC) and polyvinylpyrrolidone were used as granulating agents along with hydrophilic matrix materials like hydroxy propyl methylcellulose (HPMC) and guar gum. The granules were evaluated for angle of repose, bulk density, compressibility index, total porosity, and drug content. The tablets were subjected to weight variation test, drug content, hardness, friability, and in vitro release studies. The granules showed satisfactory flow properties, compressibility, and drug content. All the tablet formulations showed acceptable pharmacotechnical properties. The results of dissolution studies indicated that formulation F1 (drug-to-HPMC, 1:4; ethanol as granulating agent) could extend the drug release up to 12 hours. In the further formulation development process, F5 (drug-

to-HPMC, 1:4; EC 4% wt/vol as granulating agent), the most successful formulation of the study, exhibited satisfactory drug release. All the formulations exhibited diffusion-dominated drug release.

Deshmukh et al., (2009) design and evaluate oral sustained drug delivery system for Metoprolol Succinate using natural hydrophilic gums such as karaya gum and xanthan gum as a release modifier. Nine batches were prepared by using karaya gum (KG) and xanthan gum (XG) in concentration of 15%, 20% and 25% alone and in combination of 2:8. Matrix tablets were prepared by wet granulation method and were evaluated. Among the formulations studied, formulation F8 containing combination of KG and XG (2:8) having concentration of 20% showed sustained release of drug for 12hrs with cumulative percent release of 99.24%. The matrix formulation F8 showed sustained release of Metoprolol Succinate by the diffusion mechanism.

Gohel et al., (2009) to fabricate modified release tablet of Metoprolol Succinate using hydroxy propyl methylcellulose (HPMC) and xanthan gum as a matrixing agent. A 3^2 full factorial design was employed for the optimization of formulation. The percentage drug released at a given time (Y_{60}, Y_{240} and Y_{720}) and the time required for a given percentage of drug to be released ($t_{50\%}$) were selected as dependent variables. The *in-vitro* drug dissolution study was carried out in PH 6.8 phosphate buffer employing paddle rotated at 50 rpm.

Moreshwar N.Kulkarni et al., (2009) validated Spectrophotometric method for the estimation of Metoprolol in bulk drug has been developed. In method Distilled water, 0.1NHcl, Phosphate Buffer6.8 were used as solvent and shows absorption

maximum at 224 nm. The Beer's law range for Distilled water, Phosphate buffer was in 5-30 µg/ml and 10-50 µg/ml for 0.1 NHCL. The method was found to be linear, accurate and precise.

Reeta *et al.,* (2009) To reduce the frequency of dose administration and to prevent nocturnal heart attack and to improve the patient compliance by developing extended release (ER) matrix tablet of Metoprolol succinate. Eight batches of ER matrix tablets of Metoprolol succinate were developed by using wet granulation technique and coated with hydroxy propyl methyl cellulose (KM 100) and hydroxyl methyl cellulose for extended release. Among the eight formulations, F8 showed extended release of drug for 20 hours with 87.1% drug release and subjected to stability studies for 3 months at 40°C/75% RH and 60°C/80%RH.

William et al., (2009) studied the effects of Metoprolol Succinate extended release vs. Amlodipine Besilate on the blood pressure, heart rate, and the rate-pressure product in patients with hypertension. The results of the study demonstrated that Metoprolol Succinate ER induced greater reductions in early morning BP, HR, and FPP than Amlodipine in middle-aged patients with Stages 1 and 2 hypertension.

Nisarur-ur-Rahman et al., (2008) reported an In vivo performance of controlled release pellets of diltiazem HCl was evaluated in vivo, in comparison with Herbesser SR. six healthy volunteers perspired in the study, conducted according to randomized, two-way parameters plasma concentration-time curve, C_{Max} T_{Max} were estimated from the plasma concentration –time profile for each volunteers. The formulations started to release their drug content immediately upon rupture of the capsules but in sustained manner

SH Lakade & MR Bhalekar, (2008) the objective of the present study was to develop hydrophilic polymer (HPMC) and hydrophobic polymer (Ethyl cellulose) based Nicorandil matrix sustained release tablet which can release the drug up to time of 24 hrs in predetermined rate. The formulation of Nicorandil matrix tablet was prepared by the polymer combination in order to get required theoretical release profile. The influence of hydrophilic and hydrophobic polymer and granulation technique on Nicorandil was studied. The formulated tablet were also characterized by physical and chemical parameters, The in-vitro release rate profile should the higher concentration of F2 polymer in tablet, the combination of hydrophilic and hydrophobic combination showed less result than use of alone. The in–vitro release data was well fit to Peppas and Hixon crowel release kinetics.

K. Kannan et al., (2007) dissolution test for sustained release capsules of Metoprolol 125 mg was developed and validated according to FDA and ICH guidelines. Metoprolol coated pellets were coated with microcrystalline wax and glyceryl distearate for slow release of drug. The dissolution method which uses USP apparatus I (Basket) with rotating at 100 rpm, 900 ml of different dissolution medium, ultra violet spectroscopy for quantification was demonstrated to be robust, discriminating and transferable. Dissolution tests conditions were selected after it was demonstrated that the Metoprolol rapidly dissolved in the aqueous media over the pH range of 1.2 to 7.4.

Hainer et al., (2007) lowering elevated blood pressure (BP) with drug therapy reduces the risk for catastrophic fatal and nonfatal cardiovascular events such as stroke and myocardial infarction. Given the heterogeneity of hypertension as a

disease, the marked variability in an individual patient's BP response, and low response rates with monotherapy, expert groups such as the Joint National Committee (JNC) emphasize the value of combination antihypertensive regimens, noting that combinations, usually of different classes, have additive antihypertensive effects. Metoprolol Succinate extended-release tablet is a beta-1 (cardio-selective) adrenoceptor-blocking agent formulated to provide controlled and predictable release of metoprolol.

A.Hamid et al., (2006) formulated and Evaluated of Once-Daily tablets of Cefpodoxime using hydroxypropyl methylcellulose. Tablets were prepared by direct compression. In vitro drug release was evaluated using USP Apparatus-II. It was found that 16.86% of the drug was released during the first hour. During the initial 9 hours, ~50% of the drug was released. After 9 hours, the release rate increased slightly, until the 21st hour, and then release slowed but continued until the 24-hour mark. Hence, the formulation can be considered as a once-daily sustained-release tablet of Cefpodoxime Proxetil.

M. Harris shoaib et al., (2006) have been developed once-daily sustained release matrix tablet of ibuprofen using hydroxypropyl methylcellulose (HPMC) as release controlling factor and to evaluate drug release parameters as per various release kinetic models. In order to achieve required sustained release profile tablets were directly compressed using Avicel pH 101 and Magnesium stearate. The formulated tablets were also characterized by physical and chemical parameters and results were found in acceptable limits. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Criteria for selecting the most appropriate model was based on linearity (coefficient of

correlation). The drug release data fit well to the Higuchi expression. Drug release mechanism was found as a complex mixture of diffusion, swelling and erosion.

Sandip et al., (2003) this studied was designed to formulate the controlled release formulation of the Tramadol hydrochloride by using the different proportions of the hydrophilic and hydrophobic polymers. The hydrophilic polymer used was HPMC and the hydrophobic polymer used was ethyl cellulose. The results reported that increase in ethyl cellulose concentration retarded the drug release from the dosage form.

Claudio et al., (2000) the goal of the present study was to evaluate the influence of the formulation and operating conditions on pellets preparation by pan technique application of powdered drug on sugar based cores .inert cores were intermittently treated with micronized drug powder and adhesive solution .drug layering by GS automated pan coating system. Core resulting in the production of pellets that can further coated by different polymers to obtain modified release formulations different procedures have been used to evaluate a series of important parameters such as initial cores weight. Speed of powder application, speed type and position of the atomizers, atomization degree, temperature and air spray. At first covered with seal coating then followed by enteric coating.

Michael r. bristow, (2000) in this article the detailed description of the angina pectoris and other related diseases were described briefly. This article also includes the drugs which are used mostly in the treatment of the angina pectoris. This deals mainly with the β-adrenergic receptor blockade in chronic heart failure. A detailed description of the use of the drug Metoprolol was also studied in this article.

Paul et al., (1992) sustained-release tablet matrix systems containing hydroxypropyl methylcellulose to physically withstand the mechanical processes involved in a reworking procedure. The authors also studied the influence of polymer chemistry (substitution), the rework procedure, powder reblending levels, and the compression force on particle-size distribution, tablet friability, and tablet hardness characteristics. Also investigated were the impact of the milling, remixing, and recompression processes on the *in vitro* drug release dissolution profiles for three model drugs, ascorbic acid, chlorpheniramine maleate, and meclizine dihydrochloride.

3. AIM AND PLAN OF WORK

Aim

The aim and of the present study is to develop a pharmaceutically stable and quality improved formulation of Metoprolol succinate extended release pellets. To achieve this goal various prototype formulation trials were formulated and the evaluated with respect to the various quality controls such as dissolution, assay and stability studies will be under taken.

The primary objective of this study is to prepare drug loaded pellets of metoprolol succinate (MS) using solution layering technology, and to give functional coating of pellets with ethyl cellulose (EC), in the present study EC is used due to its convenient film formability, good physicochemical properties and minimum toxicity. HPMC confers the film a more hydrophilic nature and alters its structure by virtue of pores and channels through which the substance can diffuse more easily to control the release properties of drug formulation. The coating parameters like batch size, pan rpm, spray pattern and temperature of the bed were optimized in order to get efficient drug loading and uniform functional coating. Metoprolol succinate is used in the treatment of hypertension, chest pain (angina pectoris) and myocardial infraction either alone or in combination with other drugs.

Pellets are of great interest to the pharmaceutical industry for various reasons. Pelletized product not only offers flexibility in dosage form design and development, but also utilized to improve safety and efficacy of bioactive agent. A multiunit pellet system (MUPS) is an approach to develop capsule formulation, capsule containing MUPS, when administered drug dispersed in it. Each pellet acts a single unit.

Consequently as a separate drug delivery system. The MUPS have god desirable distribution characteristics, reproducibility, transit time and reduce chance of localization of drug delivery. It is having less prone to adherence to the intestinal walls, naso-gastric and gastromy tubes and giving predictable delivery of the product to the site of drug release.

Plan of Work

- Literature collection.
- Selection of drug and excipients.
- Pre-formulation studies.
- Compatibility studies.
- Formulation and evaluation of core pellets.
- Formulation and evaluation of coated pellets
- Evaluation of pellets loaded in capsules.
- Stability studies.
- Kinetic studies.

4. MATERIALS AND METHODS

4.1 List of materials

The materials which are used in this formulation and evaluation are illustrated in the following table.

Table 5: List of the materials used in the formulation

S.No.	Material	Manufacture
1	Metoprolol succinate	Hetero drugs limited, Hyderabad.
2	Mannitol	signet chemicals, mumbai
3	HPMC	Aurolab, Mudhurai.
4	Isopropyl alcohol	FMC biopolymer
5	Ethyl cellulose M50	FMC biopolymer
6	Sodiumlauryl sulphate	Ranq. Remedies Pvt.Ltd
7	Iron oxide	Colorcon Asia Pvt Ltd.

4.2 List of equipments

The equipments which are used in the formulation and evaluation are illustrated below in the following table.

Table 6: List of equipments used in the formulation

4.3

S.No.	Equipment	Manufacturer
1	Electronic balance.	Sartorius LA120S
2	Sieves.	Retsec ASL00
3	Tapped density meter.	Electrolab ETD-1020
4	Conventional coating pan or spray gun.	Rinak, kalweka HD410AC
5	Fluidized bed coater.	Row land chem. Machines pvt ltd.
6	Hardness tester.	Pharmatest PTB-311E
8	Dissolution test apparatus.	Elecctro lab USP XXII
9	Homogenizer.	Chamunda pharma machinery pvt. Ltd.
10	Fluidized bed dryer.	Rowland chem. Machines pvt. Ltd.
11	Peristaltic pump.	Enertech electronics pvt. Ltd.
12	Disintegration tester	Electro lab ED-2L
13	Overhead stirrer.	Remi motors Bombay RQG-129D
14	Moisture balance or LOD apparatus.	Sartorious
15	Vernier calipers.	Mitulya absolute
16	Capsule filling machine.	Palm CFM 2005
17	Stability chambers	Thermo lab standard

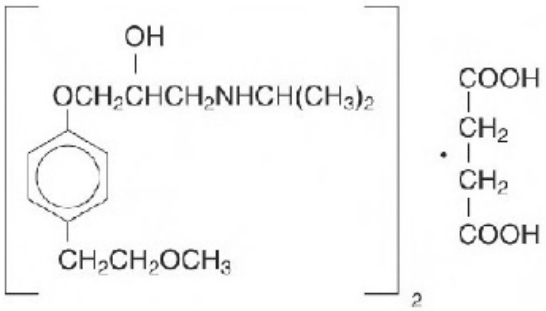
Drug profile

Metoprolol succinate

Metoprolol succinate is used for a number of conditions like hypertension, angina pectoris, acute myocardial infarction, supra-ventricular tachycardia, ventricular tachycardia, congestive heart failure and prevention of migraine headaches. Due to its selectivity in blocking the β1 receptors in the heart, metoprolol is also prescribed for off-label use in performance anxiety, social anxiety disorder and other anxiety disorders.

Metoprolol is a selective β1 receptor blocker used in treatment of several diseases of the cardiovascular system, especially hypertension. The active substance metoprolol is employed either as metoprolol succinate or metoprolol tartarate (where 100 mg metoprolol tartarate corresponds to 95 mg of metoprolol succinate). The tartarate form is an immediate-release and the succinate form is an extended- release formulation (k.kannan et al, 2007).

Figure 12: Structure of Metoprolol succinate



Empirical formula **:** $[(C_{15}H_{25}NO_3)_2.C_4H_6O_4]$

IUPAC name **:**±1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy] -2-propanal succinate

Table 7: Physico-chemical properties of Metoprolol succinate

Parameter	Characteristic
Description	White crystalline powder
Chemical name	±1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanal succinate
Molecular formula	$C_{19}H_{30}NO_7$
Molecular weight	652.8
Solubility	Freely soluble in water. Soluble in methanol. Sparingly soluble in ethanol. Slightly soluble in dichloromethane and 2-propanol. Insoluble in ethyl-acetate, acetone, diethyl ether and heptane.
Functional category	In the treatment for hypertension angina pectoris and heart failure.
Pharmacopoeial status	British pharmacopoeia (BP), European pharmacopoeia (EP) and United states of America pharmacopoeia (USP).
Storage conditions	Store at room temperature (25°C /77°F) away from light and moisture. Do not store in wet places.

Site and mode of action

The β-adrenergic blocking agents decrease the oxygen demands of the myocardium by lowering both the rate and the force of contraction of the heart. They suppress the activation of the heart by blocking β-1 receptors, and they reduce the work of the heart by decreasing cardiac output and blood pressure. The demand for oxygen by the myocardium is reduced both during exertion and at rest.

The mechanism of action of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed:

1) Competitive antagonism of catecholamines at adrenergic neuron sites (especially cardiac), leading to decreased cardiac output.

2) A central effect leading to reduced sympathetic outflow to the periphery.

3) Suppression of rennin activity.

Pharmacokinetics

Absorption and Distribution

The drug is absorbed rapidly from the intestine and it is completely absorbed. Plasma levels following oral administration of conventional metoprolol tablets approximate 50% of levels and crosses the blood-brain-barrier and has been reported in the CSF in a concentration of 78% of the simultaneous plasma concentration. The drug is also rapidly metabolized extensively in the liver. Plasma levels achieved are

highly variable after oral administration. Only a fraction of the drug (about 12%) is bound to human serum albumin.

Metabolism and Excretion

Metoprolol undergoes α-hydroxylation, O-demethylation and N-dealkylation as a substrate of the cytochrome liver enzymes CYP2D6 and a small percentage by CYP3A4. Metoprolol is a racemic micture of R and S en-antiomers and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereo-selective metabolism. Elimination undergoes mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 hrs to 7 hrs and less than 5% of an oral dose of metoprolol is excreted unchanged in urine, the rest is excreted by the kidneys as metabolites. The metabolites do not have any beta-blocking activity.

When metoprolol is administered intravenously, the unchanged drug excreted through urine is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Therefore no reduction in metoprolol succinate dosage is usually advised in patients with chronic renal failure.

Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% in Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Poor metabolizers and extensive metabolisers who use CYP2D6 inhibiting drugs will have increased metoprolol blood levels and thus decreasing metoprolol's cardio-selectivity.

The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following Metoprolol succinate administration.

Table 8: Pharmacokinetics and Pharmacodynamics of Metoprolol succinate

Parameters	Data
Tmax (hrs) (R)-Metoprolol (S)-Metoprolol	1.0±0.3 (hr) 1.0± 0.3 1.0± 0.3
Auc (ng.h/ml) (R)-Metoprolol (S)-Metoprolol (S)/(R) AUC ratio	 169± 155 279± 237 1.72± 0.27
Bioavailabilty	12%
Cmax (ng/ml) (R)-Metoprolol (S)-Metoprolol	 52± 49 = 0.52±0.49 mcg/ml 76± 57 = 0.76±0.57 mcg/ml
Biological half life	3-7hrs
Site and mechanism of absorption	GIT.
Serum protein binding	Small portion of the drug (12%) is bound to serum albumin.
Route of metabolism	Hepatic via CYP2D6, CYP3A4
Metabolites	Alpha-hydroxy-metoprolol and O-demethylmetoprolol.
Activity of metabolites	Alpha-hydroxy-metoprolol has β blockade action.
Route of excretion	Renal

Route of administration	Oral
Indications	Angina pectoris, hypertension and myocardial infarction.

Pediatrics

The pharmacokinetic profile of Metoprolol succinate was studied in 120 pediatric hypertensive patients (6-17 yrs of age) receiving dose ranging from 12.5 to 200mg once daily. Age, gender, race and ideal body weight had no significant effects on metoprolol pharmacokinetics. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight. Metoprolol pharmacokinetics have not been investigated in patients < 6yrs of age.

Adverse Effects

Central Nervous System

The Metoprolol succinate affects the central nervous system. Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported

Cardiovascular system

The Metoprolol succinate affects the central nervous system. Shortness of breath and bradycardia has occurred in approximately 3 of 100 patients. Cold extremities, arterial insufficiency, usually of the Raynaud type, palpitations,

congestive heart failure, peripheral edema, syncope, chest pain, and hypotension have been reported in about 1 of 100 patients.

Gastrointestinal

Metoprolol succinate also effects the the gastro intestinal tract in higher doses. Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders, and heartburn have been reported in about 1 of 100 patients.

Dosage and Administration

The drug should be taken as prescribed by the physician. The drug is available in the form of immediate and extended release tablet intended for either multiple doses per day or once-a-day administration.

Contraindication

Metoprolol generally is contraindicated for the treatment of acute myocardial infarction in patients with heart rates of less than 45 beats per minute, heart block greater than first-degree (PR interval ≥0.24 second), systolic blood pressure <100 mm Hg, or moderate-to-severe heart failure.

Drug interactions

Catecholeamine depleting drugs

Catecholeamine-depleting drugs (eg, reserpine, monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Obese patients treated with Metoprolol succinate plus a catecholeamine depletor for

evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypertension.

CYP2D6 inhibitors

Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metaboliser phenotype 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, co-administration of propafenone 150 mg t.i.d with immediate release metoprolol 50 mg t.i.d resulted in two to five fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardio-selectivity of metoprolol.

Digitalis, Clonidine and Calcium channel Blockers

Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant ude with beta clockers can increase the risk of bradycardia. If clonidine and a beta blocker, such as metoprolol are co-administered, withdraw the beta-blocker several days before the gradual withdrawal of clonidine because beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped.

Hypertension and Angina Cardiac Failure

Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further

depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, extended release metoprolol succinate should be administered cautiously. Both digitalis and extended release metoprolol succinate slow AV conduction.

Excipients profile

Sugar spheres

Table 9: Characteristics of sugar spheres

Synonyms	Non pareil, NPTAB, Nu-Core, Nupareil, sugar seeds and suglets.
Description	These are approximately spherical granules of a labeled nominal size range with a uniform diameter.
Functional categories	Tablet and capsule diluents.
Stability and storage conditions	Sugar spheres are stable when stored in a well-closed container in a cool dry place.

Method of manufacture	Sugar spheres are prepared from crystalline sucrose, which is cored using sugar syrup and a starch dusting powder.
Applications	Sugar spheres are mainly multi-particulate sustained release formulations. Complex drug mixture contained in a single dosage form can be prepared by coating the drugs onto different batches of sugar spheres with different protective polymer solutions.

Mannitol

Table 10: Characteristics of Mannitol

Synonyms	Mannite, Pearlitol, manna sugar and cordycepic acid.
Empirical formula	$C_6H_{14}O_6$
Description	Mannitol occurs as white, odorless, crystalline powder or free flowing granules and sweet in taste.
Functional category	Sweetening agent and tablet and capsule diluent, and tonicity agent.
Solubility	Solvent at 20°C Solution — Solublity Ethanol — 1 in 8 Ether — practically insoluble Water — 1 in5.5
Loss on drying	0.3%

Melting point	166-168°C
Stability and storage conditions	Stable in dry state and in aqueous solution. Should be stored in a well closed container, in a cool and dry place.
Incompatibilities	Precipitation has been reported to occur between 25%w/v mannitol solution with plastic.
Applications	It is used as a Diluent also suggested as plasticizer in a soft gelatin capsule, granulation containing agent, mannitol have the advantage of being dried easily.

Hydroxy Propyl Methyl Cellulose

Table 11: Characteristics of Hydroxy Propyl Methyl Cellulose (HPMC)

Synonyms	Methocel and hypromellose.
Description	White or similar white fibrous or grain powders, no odor was observed.
Functional categories	Densifiers, dispersing agent, emulsifying agent, lubricator and film former used as rheology modifier as well as water retaining agent for film formation, synthetics adhesives as well as tablet coating, controlling polymer, Stabilizing agent, binder and viscosity enhancer
Solubility	Slightly insoluble in ethanol without water, diethyl ether, acetone, it swells in cold water and forms a clear or tiny turbid colloid solution.
Loss on drying	≤5%.
Stability and storage conditions	It is chemically and physically stable at ambient temperature for at least 3–4 years and for 2–3 months at 40°C and 75% relative humidity. It is

	stable on exposure to UV light for up to 3 months at 25°C and 70% relative humidity. In general, hypromellose phthalate is more stable than cellulose acetate phthalate. At ambient storage conditions hypromellose phthalate is not susceptible to microbial attack.
Melting point	Brown at 190 - 200°C and then char at 225 - 230°C.
Incompatibilities	Incompatible with strong oxidizing agents.
Applications	It can be used as densifiers , dispersing agent, emulsifying agent, lubricator and film former etc. It can be used in food and in cosmetics, and daily chemical industries too

Isopropyl alcohol

Table 12: Characteristics Isopropyl alcohol

Synonyms	Isopropanol, propan-2-ol, 2-propanol or the abbreviation IPA, propan-2-ol, diethyl cardinal, isopropanol, petrohol, 2-propanol.
Empirical formula	C_3H_8O
Description	It is a clear colorless, mobile, volatile, flammable liquid with a characteristic spirituous odour resembling that of a mixture of ethanol and acetone, it has a slight bitter taste.
Functional categories	Solvent, disinfectant.

Solubility	miscible in water, benzene, chloroform, ethanol, ether and glycerin soluble in acetone and insoluble in salt solutions.
Moisture content	0.1-13%w/w commercial grades 13%w/w.
Melting point	–89 °C
Stability and storage conditions	Store in well-closed container in a cool and dry place.
Applications	Solvent for coatings or for industrial processes. Isopropyl alcohol in particular is popular for pharmaceutical applications

Ethyl cellulose

Table 13: Characteristics of Ethyl cellulose

Synonyms	Acquacoat ECD, Aqualon E462, Ethocel and Surelease
Empirical formula	$C_{12}H_{23}O_6 (C_{12}H_{22}O_5)_n C_{12}H_{23}O_5$
Description	The main use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation. It is tasteless, free flowing, white to tan colored powder.
Functional categories	Plasticizer, solvent, tablet and capsule lubricant, coating agent, flavoring agent, fixative, tablet binder filler and viscosity increase agent.
Solubility	Dispersible in water and soluble in Ethers, freely soluble in chloroform methyl acetate. Insoluble in

	glycerin.
pH	3 – 11
Loss on drying	< 3%
Melting point	129–133°C
Density	0.4 g/cm^3
Stability and storage conditions	Chemically stable, stored in well-closed container in a cool and dry place. Slightly absorbs moisture (hygroscopic). Resists the alkalis, salt solutions acidic materials more sensitive.
Applications	**Use** — **Concentration (%)** Micro encapsulation — 10.0–20.0 Sustained-release tablet coating — 3.0–20.0 Tablet coating — 1.0–3.0 Tablet granulation — 1.0–3.0

Yellow oxide

Table 14: Characteristics of Yellow oxide

Synonyms	Iron oxide, red oxide and ferric oxide hydrate.
Empirical formula	$Fe_2O_3 \cdot H_2O$
Description	Solid material color ranges from yellow through dark-brown to black. It is also used in aquarium

	water treatment as a phosphate binder.
Functional categories	Pigment, coloring agent.
Solubility	In-Soluble in water.
Melting point	1565°C
Stability and storage conditions	Store in a clean, dry area at ambient temperature in original unopened containers. Conditions of high humidity may require storage in a controlled environment.
Incompatibilities	Not compatible with hydrazine, calcium hypochlorite, per-formic acid and bromine pentafluoride.
Applications	It is used in cosmetics, tattoos and as coloring agent in pharmaceutical industry.

Sodium lauryl sulphate (SLS)

Table 15: Characteristics of Sodium lauryl sulphate (SLS)

Synonyms	Sodium dodecyl sulfate (SDS or NaDS), Sodium monododecyl sulfate, Sodium lauryl sulfate, Sodium monolauryl sulfate, Sodium dodecanesulfate, dodecyl alcohol, hydrogen sulfate, sodium salt, n-dodecyl sulfate sodium and Sulfuric acid monododecyl ester sodium salt.
Empirical formula	$CH_3(CH_2)_{11}OSO_3Na$

Description	White crystalline flakes
Functional categories	Surfactants, Surface-active agents, wetting agents, foaming agents, dispersing agents and emulsifying agents.
Solubility	In-Soluble in water
Loss on drying	5%
Melting point	206°C
Stability and storage conditions	Store at room temperature, Keep away from light
Incompatibilities	Incompatible with strong oxidizers, cationic materials and with acids pH less than 2.5.
Applications	It is used as a disintegrant due to its surfactant and wetting properties, removal of oily stains and residues. It is used in toothpastes, shampoos, shaving foams and bubble bath formulations in part for its thickening effect and its ability to create lather. It is also used in lysing cells during DNA extraction.

4.3 Pre-formulation studies

Pre-formulation testing was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Objective of pre-formulation study

Pre-formulation studies on active pharmaceutical ingredients (API), inactive ingredients (Excipients), and their combinations were carried out to meet the following purposes

1. To finalize specifications of active pharmaceutical ingredients (API).
2. To study the compatibility between active and inactive ingredient.
3. Characterization of reference product.

For any drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug like physical appearance, solubility, bulk density, tapped density, compressibility, melting point, molecular weight, sieve analysis

Scope

The use of pre-formulation parameters in the manufacturing of the pharmaceutical dosage forms maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

The pre-formulation study can be divided into two sub-classes

1. API characterization.
2. Compatibility study.

Active pharmaceutical ingredient (API) characterization

Organoleptic evaluation

These are preliminary characteristics of any substance before going for the manufacturing process of the dosage forms. These studies are useful in identification

of specific material by comparing their characters with the required characters. Following physical properties of API were studied.

a. Color
b. Odor
c. Taste

Solubility analysis

The solubility analysis is done for the drug. These analysis are done to know the solubility characters of the drug and to select the best vehicle or diluent in which the drug can be dissolved or suspended to form the best pharmaceutical dosage form. The solubility characters of the present drug are done and the results are given in the following table.

Physical characteristics

Loss on drying

This is specified in EP, BP and USP. Although the loss in weight, in the samples so tested, principally is due to water, small amount of other volatile materials will a contribute to the weight loss. The moisture balance combines both the drying process and weight recording, it is suitable where large numbers of samples are handled and where a continuous record of loss in weight with time is required (Milo Gibladi,2009) .

1 to 2 gm of sample of metoprolol succinate was accurately weighed and the powder was kept in a moisture balance apparatus for 5 min at 106°C and the moisture content was calculated.

Lod(%)= ((initial wt-final wt)/initial wt))*100

(Limit= NMT 0.25%)

Determination of bulk density and tap density

An accurately weighed quantity of the powder (W) was carefully poured into the granulated cylinder and volume (Vo) was measured. Then the graduated cylinder was closed with lid. Set into the density determination apparatus (bulk density apparatus) the density apparatus was set for 500 taps, 750 taps and 1250 taps. After that the volume (Vf) was measured and continued the operation till the two consecutive reading were equal. The bulk density and the tapped density were calculated using the formulas (James, 1999).

$$\textbf{Bulk density} = W / V_o$$

$$\textbf{Tapped density} = W / V_f$$

Where, W = weight of the powder

V_O = initial volume

V_F = final volume

Compressibility index and Hausner's ratio

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast and popular methods of predicting powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder (Annon et al., 2004).

% Compressibility = ($P_t - P_O / P_t$) x 100

Where, P_t = Tapped density and

P_O = Bulk density

Hausner ratio = Tapped density/Bulk density

Table 16: Standard values of Hausner ratio and Compressibilty index

S.No	Hausner ratio	Compressibility index	Flow character
1	1.00-1.11	≤10	Excellent
2	1.12-1.18	11-15	Good
3	1.19-1.25	16-20	Fair
4	1.26-1.34	21-25	Passable
5	1.35-1.45	26-31	Poor
6	1.46-1.59	32-37	Very poor
7	>1.60	>38	Very very poor

Angle of repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter-particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

Tan = h/r

$$\theta = Tan^{-1} h/r$$

where, h = height, r = radius and θ = angle of repose.

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed. Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of powder.

Table 17: Standard values of angle of repose

Flow property	Angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate/vibrate	46-55
Very poor	56-65
Very, very poor	>66

Sieve analysis

The main aim of sieve analysis was to determine the different size of drug particles present. Series of standard sieve were stacked one above the other so that the sieves with larger pore size (less sieve number) occupy top position followed by sieve of decreasing pore size (large sieve number) towards the bottom.

Procedure

A series of sieves were arranged in the order of their decreasing pore diameter (increasing sieve number) i.e. sieve no. 20, 30, 40, 60 100, 120 and 200. 100 gms of the drug was weighed accurately and transferred to sieve number 20 which were kept on top. The sieves were shaken for about 5-10 minutes then the drug retained on each sieve were taken, weighed separately and expressed in terms of percentage.

Compatibility studies by IR

One of the requirements for the selection of suitable excipients or carriers for pharmaceutical formulation is its compatibility. Therefore in the present work a study was carried out by using infrared spectrophotometer to find out if there is any possible chemical interaction of Metoprolol Succinate drug with HPMC and ethylcellulose.

Procedure

Weighed amount of drug (1 mg) was mixed with 99 mg of potassium bromide (dried at 40°C - 50°C). The mixture was taken and compressed under 7-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned in IR spectrophotometer in the range of 2000 cm^{-1} to 500 cm^{-1}.

Drug excipient compatibility study by force degradation method

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf-life of product or any other unwanted effects on the formulation.

Procedure

Drug is mixed with excipients in different ration. 15gm of blend is prepared which is filled in 3 vials. Observations for physical appearance are made at zero weeks, 2 weeks and 4 weeks. These mixtures were kept in a 5ml glass white colored vials and packed properly. These vials are exposed to the different conditions 40°C at 75%RH, 60°C and 2-8°C. The samples are taken at the regular intervals and they are tested visually for any color change in the product, if any color change exists then it shows that the drug is not compatible with the excipient. Then the excipients have to be changed and again should be tested with other excipients to see compatibility between them. if any color change does not occur then they can be formulated to form a formulation. This process continues until we get the compatible excipients with the drug. The samples are taken monthly when kept at 40°C, the samples are taken at every 15 days when the samples are kept at 60°C and monthly when the samples are kept between 2°-8°C. Then the samples are taken and examined visually for the color change.

4.4 Formulation development

Metoprolol succinate extended release capsules were prepared. The process was displayed in the below flow chart.

Flow chart for manufacturing of extended release capsules

1. Preparation of core pellet

Preparation of core mixture suspension (drug and excipients)

↓

Loading of sugar spheres in to fluid bed coater

↓

Coating of metoprolol succinate

↓

2. Sub Coating

Dissolve the required amount of Ethyl cellulose in Isopropyl alcohol

Stir it for 5 minutes to form uniform solution

↓

Spray the coating solution by using Fluidized bed coater

↓

Maintain the required conditions in coater

↓

Collect #16 passed #20 retained fines

↓

Filling of the pellets into capsules.

Preparation of pellets

Preparation of core mixture suspension

The required quantities of the drug and the excipients are taken approximately and mixed in water. It is stirred until a uniform suspension is formed.

Preparation of core drug pellets

The non-pariel seeds (sugar spheres 24/30) are accurately weighed and transferred into the coating pan. The drug suspension is sprayed on the non-pariel seeds at the given set of conditions which are given below. The coating was done by the solution layering technique.

Drying of the core drug pellets

Then these pellets are dried at 40-45°C for 6-8 hrs. The moisture content should be less than 2% in the pellets. Then the pellets are sifted and passed through the sieve and the pellets of size 14/20 are collected and are taken for coating with the polymer for sustained release of the drug.

Preparation of sub coating material

The sub coating material is prepared by dissolving the required quantities of the ethyl cellulose in isopropyl alcohol and it is stirred for 15min to form a uniform solution. Then this is taken to coat the core drug pellets.

Coating of the core drug pellets

The sub coating solution was sprayed on the core pellets in the fluid bed coater. This makes the sustained release layer around the core pellet. The conditions which are required for the coating are given below.

Drying of the core drug pellets

The pellets after sub coating are taken and they are dried. Then the pellets are taken and are passed through the sieve of required ranges and the required pellets are collected. The pellets of size 16/20 are collected.

Filling of core pellets into the capsules

The obtained pellets are taken and are transferred into the capsule of suitable size. each capsule should be with drug equivalent to label claim.

Table 18: Composition of the core pellets in the formulation trials.

S. No	Ingredients (mg)	MSER CF1	MSER CF2	MSER CF3	MSER CF4	MSER CF5	MSER CF6	MSER CF7	MSER CF8
1	Metoprolol succinate	50	50	50	50	50	50	50	50
2	Manitol	12.5	12.5	12.5	12.5	12.5	125	125	12.5
3	Sodium lauryl sulphate	10	9.5	9	8.5	8	7.5	7	6.5
4	Sugar spheres (24/30)	25	25	25	25	25	25	25	25
5	HPMC	1.5	2	2.5	3	3.5	4	4.5	5
6	Yellow oxide	1	1	1	1	1	1	1	1
	Total (mg)	100	100	100	100	100	100	100	100

Table 19: Composition of the coating material for the optimized core pellet

S.No	Ingredients	MSE R F1	MSER F2	MSE R F3	MSE R F4	MSE R F5	MSE R F6	MSE R F7	MSE R F8
7	Ethyl cellulose (mg)	2%	2.5%	3%	3.5%	4%	4.5%	5%	5.5%
8	Iso propyl alcohol (ml)	65ml	85ml	100ml	115ml	135ml	150ml	165ml	185ml

Fluidized bed processor was operated with following conditions

- Inlet temperature - 40-45°C
- Bed temperature - 35-40°C
- Spray rate - 5 rpm
- Air pressure - 1-1.5 pascals

4.5 Evaluation of drug coated and polymer coated pellets

Description

For checking the appearance of pellets 20 gm of pellets taken From respective batch and observed for the color and shape of the pellets

Hardness

Hardness tester was used to determine the hardness of pellets. The test pellet was held between the edge of the fixed and movable part of the instrument. The scale was adjusted by sliding so that the zero on the scale coincides with the pointer. The adjustable knob is slowly moved till the pellet breaks. The pressure indicated on the dial was in newtons (N). The hardness test was performed by pharmatest hardness tester. After breaking of the pellets the display is read and the reading is noted down.

Flow properties

Determination of bulk density and tap density

An accurately weighed quantity of the powder (W) was carefully poured into the granulated cylinder and volume (Vo) occupied by the dry powder is measured. From this the bulk density of the sample can be calculated by using the formula given below. Then the graduated cylinder was closed with lid. Set into the density determination apparatus, the density apparatus was set for 500 taps, 750 taps and

1250 taps. After the procedure for each set of taps the cylinder is taken and the volume (V_f) occupied by the dry powder is measured and continued the operation till the two consecutive reading were equal. The tapped density is calculated using the formula.

$$\textbf{Bulk density} = W / V_o$$

$$\textbf{Tapped density} = W / V_f$$

Where, W = weight of the powder
V_O = initial volume
V_f = final volume

Compressibility index and Hausner ratio

In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder. The formulas which are used for calculating the compressibility index and the Hausner's ratio is given below.

$$\textbf{\% Compressibility} = (P_t - P_O / P_t) \times 100$$

Where, P_t = Tapped density and
P_O = Bulk density

Hausner ratio = Tapped density/Bulk density

The standard values for the compressibility index and the Hausner's ratio is given during the discussion of pre-formulation studies of the pure drug

Angle of repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter-particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$$\mathbf{Tan\ \theta = h/r}$$

$$\mathbf{\theta = Tan^{-1}\ h/r}$$

Where, θ = angle of repose, h = height and r = radius.

Procedure

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed. Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of powder.

The standard values for the compressibility index and the Hausners ratio is given during the discussion of pre-formulation studies of the pure drug

Sieve analysis

The main aim of sieve analysis was to determine the different size of drug particles present. Series of standard sieve were stacked one above the other so that the sieves with larger pore size (less sieve number) occupy top position followed by sieve of decreasing pore size (large sieve number) towards the bottom.

Procedure

A series of sieves were arranged in the orde of their decreasing pore diameter (increasing sieve number) i.e. sieve no. ASTM 40, 60, 80, 100 with 40gms of drug were weighed accurately and transferred to sieve 40 which were kept on top. The sieves were shaken for about 5-10min. then the drug retained on each sieve were taken, weighed separately and expressed in terms of percentage.

Assay

Preparation of buffer

6.8 pH Phosphate buffer: dissolve 6.8gm of potassium di-hydrogen phosphate in purified water. Make up the volume upto 1000ml by purified water and adjust the pH by using sodium hydroxide solution.

Preparation of standard

Aqueous solutions of phosphate buffer of pH 6.8 is prepared as per USP25. Standard drug solution was prepared (1 mg/ml) in Phosphate buffer 6.8. Metoprolol (100mg) was dissolved in 10 ml of Phosphate buffer 6.8 and the total volume was brought to 100ml with phosphate buffer 6.8 to obtain stock solution. Stock solution was further diluted to obtain 5-30 µgm/ml with phosphate buffer 6.8.

Preparation of sample

MS pellets 50mg were transferred into volumetric flask and added upto 50ml with pH 6.8 phosphate buffer. The amount of drug content was estimated UV spectrophotometrically. Content uniformity test was evaluated for the formulation by collecting samples from three different portions of the bulk.

Dissolution Profile

Buffer preparation

6.8 pH Phosphate buffer: dissolve 6.8gm of potassium di-hydrogen phosphate in purified water. Make up the volume up to 1000ml by purified water and adjust the pH by using sodium hydroxide solution.

Standard curve

Preparation of stock solution: Aqueous solutions of phosphate buffer of pH 6.8 is prepared as per USP25. Standard drug solution was prepared (1mg/ml) in Phosphate buffer 6.8. Metoprolol (100mg) was dissolved in 10ml of Phosphate buffer 6.8 and the total volume was brought to 100ml with phosphate buffer 6.8 to obtain stock solution.

Stock solution was further diluted to obtain 5-30 µgm/ml with phosphate buffer 6.8. Standard solutions of Metoprolol succinate (10µgm/ml) in phosphate buffer is scanned in the 200-700nm range to determine the maximum absorbance (λmax). The λmax was determined in the solvent and found to be 224nm.

The absorbance was measured at 224nm against phosphate buffer 6.8 as blank. The calibration curve was plotted in the concentration range of 5-30 µgm/ml of Metoprolol succinate in phosphate buffer 6.8 .

***In- vitro* drug release studies**

The in vitro drug release studies were performed for marketed product using dissolution medium as 6.8 pH Phosphate buffer volume 900 ml at 50 rpm, USP II apparatus. By using UV-spectrophotometer at 224 nm.

Dissolution

The samples are taken from the formulated trial batches. These samples are filled in the capsules. Then these capsules are subjected to the in-vitro dissolution tests. The samples are taken at specific intervals and the percentage of drug release is calculated. Then the cumulative percentage drug release of the different trials are compared with that of the Innovator drug release profile. The drug release profile of the trial which matches with that of the innovator drug release profile is taken and the evaluation tests for this optimized formulation is carried out. The dissolution test is carried by considering the following parameters.

Dissolution parameters

- Media - 6.8 pH phosphate buffer.
- Apparatus - USP II (paddle)
- RPM - 50
- Amount of media - 500 ml
- Temperature - 37ºC ±0.5
- Time - Upto 20hrs for polymer coated pellets.
  Upto 1hr for drug coated pellets.

4.6 Evaluation of capsules

Weight variation test

Individual weights of 20 capsules were taken and the average weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{(Weight of capsule-Average weight)}}{\text{Average weight of capsules}} \times 100$$

Weight variation should not be more than 7.5%.

Disintegration test

The disintegration test is done to know the time needed for the disintegration of the capsule shells and to release its components into the buffer solution. For the hard gelatin capsules the disintegration time limit shall not be more than 30mins.

Assay

Preparation of buffer

6.8 pH Phosphate buffer: dissolve 6.8gm of potassium di-hydrogen phosphate in purified water. Make up the volume upto 1000ml by purified water and adjust the pH by using sodium hydroxide solution.

Preparation of standard

Aqueous solutions of phosphate buffer of pH 6.8 is prepared as per USP25. Standard drug solution was prepared (1mg/ml) in Phosphate buffer 6.8. Metoprolol (100mg) was dissolved in 10ml of Phosphate buffer 6.8 and the total volume was brought to 100ml with phosphate buffer 6.8 to obtain stock solution.Stock solution was further diluted to obtain 5-30 µgm/ml with phosphate buffer 6.8.

Preparation of sample

MS pellets 50mg were transferred into volumetric flask and added upto 50ml with pH 6.8 phosphate buffer. The amount of drug content was estimated UV

spectrophotometrically. Content uniformity test was evaluated for the formulation by collecting samples from three different portions of the bulk.

Loading of metoprolol succinate pellets in capsules

Objective

The primary objective is to prepare Metoprolol succinate capsules of 25 mg strength. This is done by taking Metoprolol succinate core pellets equivalent to 25mg of Metoprolol succinate from the formulation MSER F7 and loading into the capsules of given appropriate size. The filling of the pellets into the capsules is done by the capsule filling machine. Then these are evaluated for the required evaluation tests.

Procedure

1. Size '2' capsules were selected for capsule formulation.
2. The pellets were loaded in hard gelatin capsules No-2 with capsule filling machine
3. Coated pellets were transferred into capsules by spreading it into equal quantities equivalent to 25 mg Metoprolol succinate.

4.7 Kinetics of drug release

The results of *in vitro* release profiles obtained for all the formulations were fitted into three models of data treatment as follows:

1. Cumulative percent drug released versus time (zero-order kinetic model).

2. Cumulative percent drug released versus square root of time (Higuchi's model).

3. Log cumulative percent drug released versus log time (Korsmeyer-Peppas equation).

Zero Order Kinetics

A zero-order release would be predicted by the following equation.

$$\mathbf{A_t = A_0 - K_0 t \ldots 1}$$

Where,

A_t = Drug release at time 't'

A_0 = Initial drug concentration

K_0 = Zero-order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

Higuchi's Model

Drug released from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$\mathbf{Q = [D\varepsilon/\tau(2A - \varepsilon C_s)\, C_S\, t]^{1/2} \ldots 2}$$

Where,

Q = Amount of drug released at time 't'

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

C_S = The solubility of the drug in the diffusion medium

ε = Porosity of the matrix

τ = Tortuosity

t = Time (hrs) at which 'Q' amount of drug is released.

Equation-2 may be simplified if one assumes that D, C_S and A are constant. Then equation-2 becomes:

$$Q = Kt^{1/2} \ldots 3$$

When the data is plotted according to equation-3 i.e., cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsmeyer and Peppas Model

The release rates from sustained release polymeric matrices can be described by the equation (4) proposed by Korsmeyer et al.

$$Q = K_1 t^n \ldots . 4$$

Q is the percentage of drug released at time't', K is a kinetic constant incorporating structural and geometric characteristics of the tablets and 'n' is the diffusional exponent indicative of the release mechanism.

For Fickian release, n=0.45 while for anomalous (Non-fickian) transport, n ranges between 0.45 and 0.89 and for zero order release, n = 0.89.

4.8 Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of

environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives.

The International Conference on Harmonization (ICH) guidelines titled "Stability Testing of New Drug substance and Products" (QIA) describes the stability test requirements for drug registration for drug registration applications in the European Union, Japan and The United States of America.

ICH specifies the length of study and storage conditions.

Table 20: Stability Storage Conditions

Study	Storage condition	Minimum time period covered by data at submission.
Long term	25ºC ± 2 ºC/ 60% RH ± 5% RH	12 months
Intermediate	30ºC ± 2 ºC/ 65% RH ± 5% RH	6 months
Accelerated	40ºC ± 2 ºC/ 75% RH ± 5% RH	6 months

Stability studies were conducted according to ICH Guidelines; the optimized formulation was packed and stored at three different conditions i.e. Long term, intermediate and accelerated conditions in a stability chamber for a period of 3 months. The samples were evaluated for assay and dissolution studies at regular intervals.

5. RESULTS AND DISCUSSION

The present study was carried out to formulate Metoprolol succinate ER pellets (25 mg). The study involves pre-formulation studies of drug and excipients, formulation and processing development along with evaluation of pellets made with the optimized formulation. Finally extended release pellets were evaluated by in-vitro methods.

5.1 Pre-formulation studies

Table 21: Preformulation studies of Metorpolol succinate pure drug

S.No	Characteristics	Results
1	Organoleptic evaluation	Color: white crystalline powder Taste: bitter Odor: characteristic
2	Solubility analysis	Freely soluble in water, soluble in methanol, sparingly soluble in ethanol and slightly soluble in dichloromethane and 2-propanol, insoluble in ethyl-acetate, acetone, diethyl ether and heptane.
3	Bulk density	0.375 gm/ml
4	Tapped density	0.5727 gm/ml
5	Compressibility index	34.55
6	Hausner's ratio	1.528
7	Loss on drying	0.19%
8	Angle of repose (°)	37.23°

The pre-formulation studies are done and the results are given in the above table. The flow property studies results showed that the drug has poor flow properties.

The solubility studies are done and it indicates that the drug is freely soluble in water and slightly soluble in alcohol.

Sieve analysis

Table 22: Sieve analysis of Metoprolol succinate pure drug

S.No.	Sieve no	Empty sieve (mg)	Sample sieve (mg)	Difference (mg)	%Retained	%Cumulative retained
1	#20	321.4	321.4	0	0	0
2	#30	328.6	328.8	0.2	0.2	0.2
3	#40	299	300	1	1	1.2
4	#60	287.2	297.4	10.2	10.2	11.4
5	#100	255	275	20	20	31.4
6	#120	274	299	25	25	56.4
7	#200	270	303.2	33.2	33.2	89.6
8	Receiver	348.8	359	10.2	10.2	99.8

Weight of smple = 100gm.

Through this analysis we came to know that as large quantity of powder was retained on sieve no. 200, which indicates poor flow of drug. Flow property and particle size are inversely proportional to each other as Metoprolol succinate has fine grade of particles, it has poor flow. In this process the particle size of the drug is also known. But due to the poor flow property of the pure drug the size of the particles is not estimated.

Drug –polymer compatibility studies by FTIR

In the compatibility studies by using the FTIR process, the drug is mixed with each excipient or polymer mostly in small quantities and they are allowed to react for some time as specified. Then the samples from these mixtures are taken and they are exposed to the IR spectroscopy. From the peaks that are obtained we can estimate the reaction between the drug and its excipients by comparing the FTIR graphs of the pure drug and the FTIR graph of the mixture. if any difference is observe then it indicates that the drug is not compatible with the excipients and we cannot further formulate the formulation using these ingredients. The results showed no major difference betweenn the FTIR pure drug graph and the the FTIR graph of the mixture, so they are said to be compatible with each other and we can further use these mixtures in the present study of formulation to formulate the Metoprolol succinate pellets. The major peaks in the FTIR spectra of the metoprolol succinate pure drug are given in the following table

Table 23: Identification peaks of Metoprolol succinate

S. No.	**Functional group**	**cm^{-1} (Wave No)**
1	0-H bending	1051.24
2	C-0 Aromatic “C”	1242.5
3	C-H aromatic def Stretching	781-842.92 3030
4	N-H Stretching	3400-3500 1558.54 – 1616.40
5	C-H alkane Stretch	2850 – 2960 1332.86

Figure 13: FTIR Spectra of Metoporolol succinate pure drug.

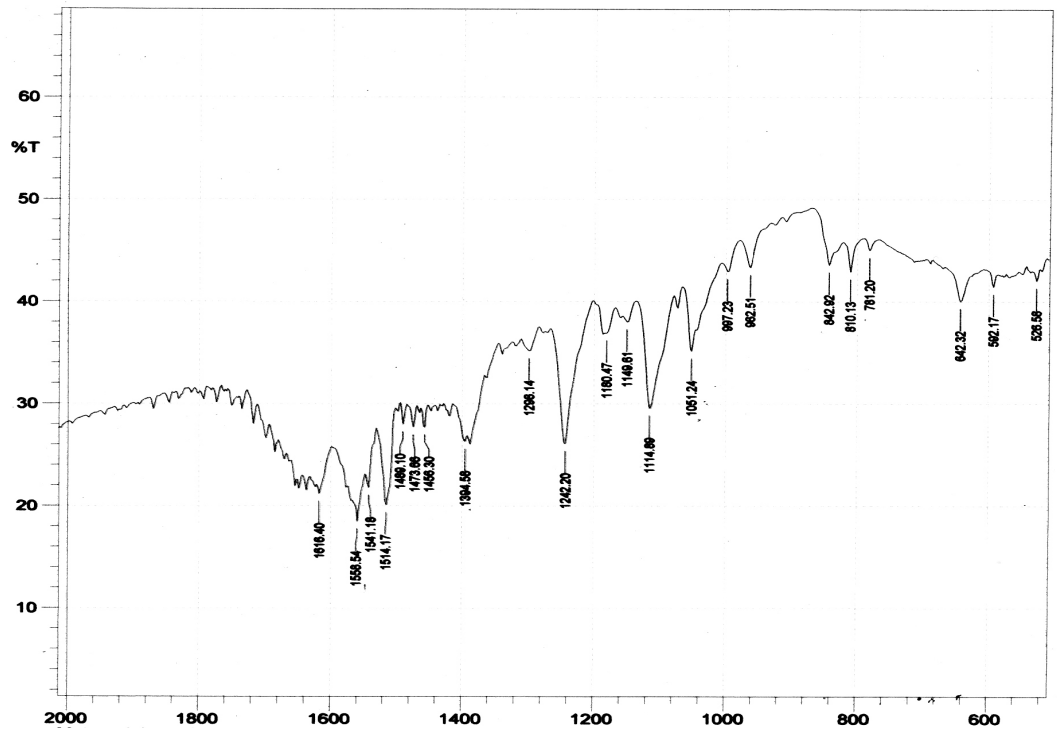


Figure 14: FTIR Spectra of Metoprolol succinate and HPMC

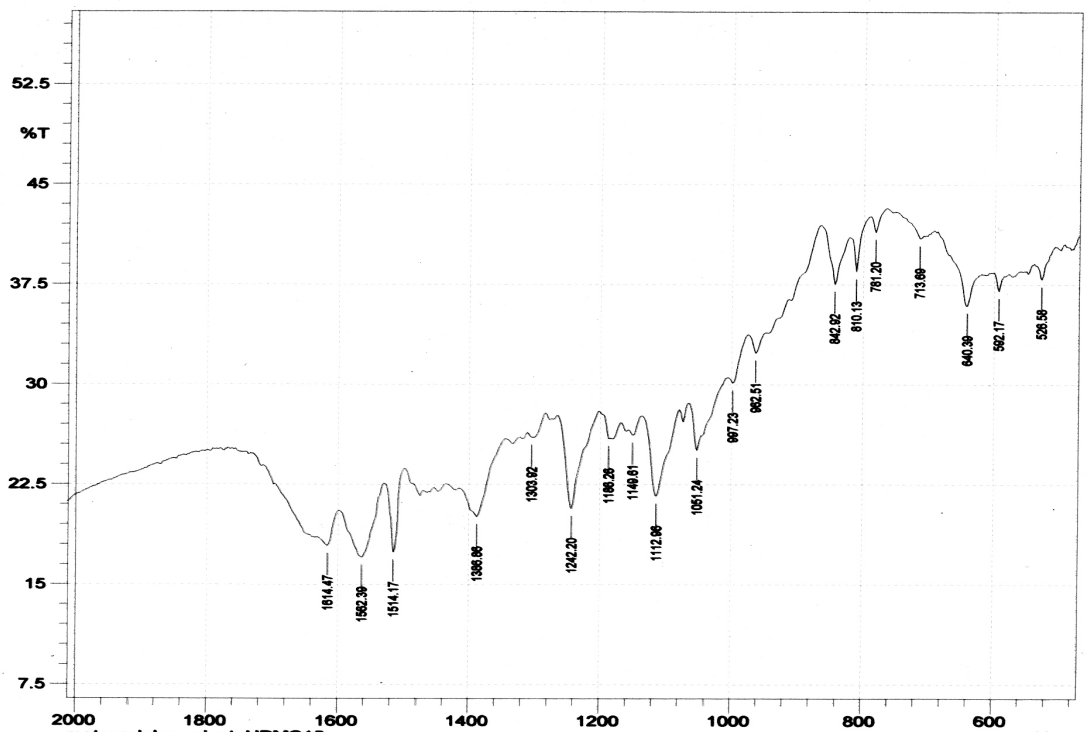
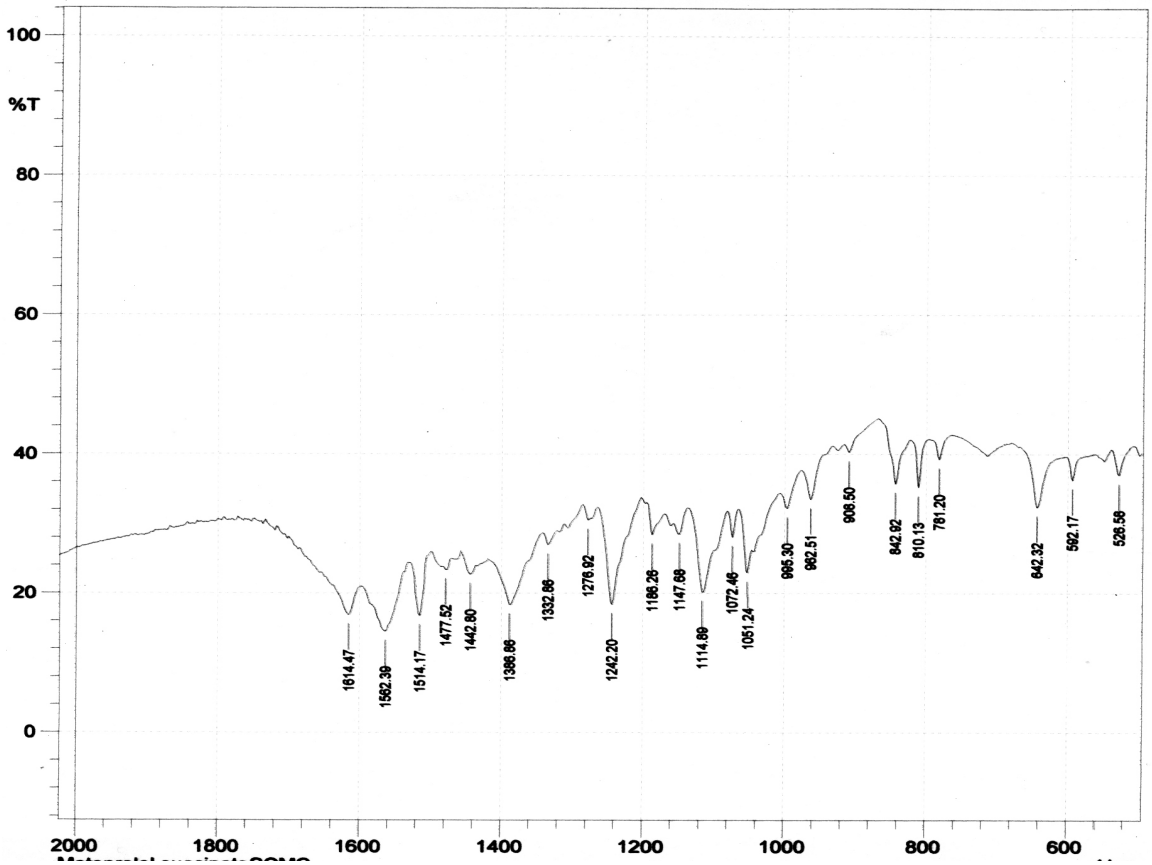


Figure 15: FTIR spectra of Metoprolol succinate and Ethyl cellulose



Drug-excipients compatibility studies

The drug–excipient compatibility studies are studies at 3 different conditions. The 3 different conditions at which the accelerated stability studies are carried out are

40°C , 75%RH for 3 months

60°C for 30 days

2-8°C for 3 months.

The samples are withdrawn at regular intervals and evaluated. The results for the last samples are given in the following table.

Table 24: Drug-excipient compatibility study of Metoprolol succinate with its excipients

S. No	Composition details	Ratio API: Expt	Observations				Conclusion
			Storage condition/duration				
			Initial (color)	40°C/75%RH	60°C	2-8°C	
				3M	30D	3M	
1	API	----	White to yellowish	NCC	NCC	NCC	Compatible
2	API+ mannitol	1:1	A white color powder	NCC	NCC	NCC	Compatible
3	API+ sodium lauryl sulphate	1:1	A white color powder	NCC	NCC	NCC	Compatible
4	API+ sugar spheres	1:1	A white color powder	NCC	NCC	NCC	Compatible

5	API+ HPMC	1:1	A white color powder	NCC	NCC	NCC	Compatible
6	API+ yellow oxide	1:1	A white color powder	NCC	NCC	NCC	Compatible
7	API+ ethyl cellulose	1:1	A white color powder	NCC	NCC	NCC	Compatible

NCC = No Color Change

By studying the Drug-excipient compatibility studies and IR spectra's the results showed that there was no interaction between the drug and its excipients, so the excipients were found to be compatible with the drug (Metoprolol succinate).

5.2 Evaluation of drug coated pellets (core pellets)

The sample of pellets were taken after the coating of the sugar spheres with the drug suspension. Then these were evaluated for shape and color visually.

Table 25: Physical characters of Metoprolol succinate optimized core pellets

S.No.	Characteristics	Results
1.	Physical appearance	Yellowish crystalline spheres.
2.	Dimension	1.2µ-1.8µ
3.	Hardness	6N
3.	Bulk density	0.38 gm/ml
4.	Tapped density	0.448 gm/ml
5.	Compressibility index	15.147%
6.	Hausner's ratio	1.178%
7	Angle of repose	33.47°

By studying the pre-formulation studies of the coated pellets, the results showed that the flow properties of the pellets are not good in the formulations MSER CF1 but as the concentration of HPMC increased the flow property was good. And there is no need to add an excipient to increase the plow properties. But in the formulation MSER CF8 the pellets showed cracks so the formulation MSER CF7 was optimized. The pellets after the formulation showed Yellowish color due to the addition of the coloring agent.

Sieve analysis

Table 26: Particle size distribution of Metoprolol succinate core pellets

S.No	Sieve number	MSER CF1 (mg)	MSER CF2 (mg)	MSER CF3 (mg)	MSER CF4 (mg0)	MSER CF5 (mg)	MSER CF6 (mg)	MSER CF7 (mg)	MSER CF8 (mg)
1	10	12.2	20.6	10.4	8.6	4.3	1.2	0	0

2	12	36.2	37.2	32.1	36.3	39.1	13.3	1.4	0.6
3	16	33.4	32	31.4	18	15.3	3.2	`2.4	1.2
4	18	12	10.2	26.1	47.1	63.3	83.3	96.2	98.2

The sieve analysis has been performed to check the size of the coated pellets, and the results revealed that the pellets are of uniform in size and they are in the size of 1.2µ - 1.8µ. The size of the pellets is determined by identifying the sieve which has allowed the pellets to pass and the sieve on which the sample is collected. The Sieve that has retained the pellets determines the minimum size of the pellets and the sieve which has allowed the pellets to pass determines the maximum size of the pellets. These results indicated that the formulations with more binder (HPMC) concentration showed better flow properties and uniform size. In the MSER CF1 the pellets were agglomerated and there was poor flow. As the concentration of the binder (HPMC) was increased and the concentration of the wetting agent was decreased (SLS) the agglomeration of the pellets were decreased and the flow properties of the pellets were increased. The formulation MSER FC7 showed best flow properties among all the formulations.

Assay of pellets

Table 27: Assay of core pellets

Character	MSER CF1	MSER CF2	MSER CF3	MSER CF4	MSER CF5	MSER CF6	MSER CF7	MSER CF8
Assay	98.56%	97.68%	98.36%	97.34%	98.64%	98.48%	99.32%	98.86%

The assay is conducted to check the purity of the sample or drug. In this test the pellets are tested for the content of the drug present in the pellets and to check

whether the drug is present according to label claim in the pellets. The results revealed that the drug content is present with in the limits of the label claim that are specified for all the formulations.

Dissolution studies

The samples are taken from the formulated trial batches. These samples are filled in the capsules. Then these capsules are subjected to the in-vitro dissolution tests. The samples are taken at specific intervals and the percentage of drug release is calculated. The drug release profile of the trial which matches with that of the innovator drug release profile is taken and the evaluation tests for this optimized formulation is carried out. The dissolution test is carried by considering the following parameters.

Dissolution parameters

- Media - 6.8 pH phosphate buffer
- Apparatus - USP II (paddle)
- RPM - 50
- Amount of media - 500ml
- Temperature - 37ºC ±0.5
- Time - Upto 1hr.
- Time interval - 10min.

Table 28: Dissolution studies of drug coated pellets (core pellets)

S.No	Time interval (min)	Cumulative % drug release							
		MSER CF1	MSER CF2	MSER CF3	MSERCF4	MSER CF5	MSER CF6	MSER CF7	MSERCF8

1	15	38.75	36.85	33.86	31.48	27.85	26.89	25.36	24.48
2	30	78.46	75.86	74.84	68.78	58.78	55.35	64.86	56.56
3	45	98.56	98.84	95.46	93.85	88.46	83.42	82.73	81.56
4	60	99.65	99.32	98.76	98.82	99.45	99.64	99.65	98.87

The dissolution studies for the drug coated pellets were conducted according to the in house specifications. the results showed that all the formulations released the drug with in one hour. The MSER CF1 released the drug with in 45min because of the more amount of the wetting agent (SLS) in it. as the SLS concentration decreased and binder (HPMC) concentration increased in the further formulations the drug released was retarded to a smaller extent.

By considering all the evaluation results the formulation with 7% Sodium lauryl sulphate (SLS) and 4.5% binder (HPMC) was optimized. Then these pellets were given polymer coating in varied proportions by using ethyl cellulose as drug release retardant polymer.

5.3 Evaluation of polymer coated pellets

Table 29: Physical characters of optimized Metoprolol succinate polymer coated pellets

S.No.	Characteristics	Results
1.	Physical appearance	Yellowish crystalline powder.
2.	Dimension	1.6nm-2nm
3.	Hardness	9N
3.	Bulk density	0.37gm/ml
4.	Tapped density	0.425gm/ml
5.	Compressibility index	11.793%
6.	Hausner's ratio	1.1317%
7	Angle of repose	28.53

By studying the pre-formulation studies of the coated pellets, the results showed that the flow properties of the pellets are good. And there is no need to add an excipient to increase the flow properties. The pellets after the formulation showed Yellowish color due to the addition of the coloring agent.

Sieve analysis

Table 30: Particle size distribution polymer coated pellets

S.No	Sieve number	MSER F1 (mg)	MSER F2 (mg)	MSER F3 (mg)	MSER F4 (mg)	MSER F5 (mg)	MSER F6 (mg)	MSER F7 (mg)	MSER F8 (mg)
1	12	0	0	0	0	0	0	0	0
2	16	8.4	7.9	2.5	1.9	1.4	4.5	2.06	2.07
3	18	3.4	2.8	1.4	1	0.97	1.6	2.48	1.45
4	20	88.2	89.3	96.1	98.03	97.8	93.39	95.46	96.48

The sieve analysis has been performed to check the size of the coated pellets, and the results revealed that the pellets are of uniform in size and they are in the size of 16µ - 20µ. The size of the pellets is determined by identifying the sieve which has allowed the pellets to pass and the sieve on which the sample is collected. The Sieve that has retained the pellets determines the minimum size of the pellets and the sieve which has allowed the pellets to pass determines the maximum size of the pellets. By

the results from the sieve analysis the it has been found that the pellets has improved flow properties and they did not agglomerate like the drug coated pellets. These also showed uniform particle size in all the formulations which indicates the uniform coating of the polymer on the drug coated pellets.

Assay of pellets

Table 31: Assay of polymer coated pellets

Character	MSER F1	MSER F2	MSER F3	MSER F4	MSER F5	MSER F6	MSER F7	MSER F8
Assay	99.45 %	99.78 %	100.43 %	99.65 %	99.86 %	99.48 %	99.86 %	99.48 %

The assay is conducted to check the purity of the sample or drug. In this test the pellets are tested for the content of the drug present in the pellets and to check whether the drug is present according to label claim in the pellets. The results revealed that the drug content is present with in the limits of the label claim that are specified for all the formulations.

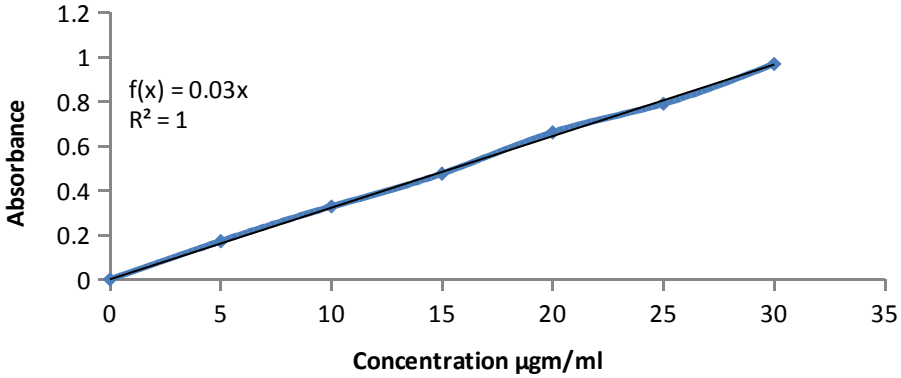
Dissolution profile

Standard graph for metoprolol succinate

Table 32: Standard plot of Metoprolol succinate

S.No	Concentration (µgm/ml)	Absorbance
1	5	0.172
2	10	0.328
3	15	0.476
4	20	0.662
5	25	0.791
6	30	0.9696

Figure 16: Standard curve of metoprolol succinate



Slope=0.032 R^2=0.999

In-vitro dissolution test

The dissolution was carried out for different experimental trials and also for the innovator. The various results that are obtained are tabulated below. The procedure for the dissolution is already given tin the materials and methods part. Dissolution studies are carried out in the following media.

Medium : phosphate buffer ph 6.8
Apparatus : USP type II (paddle)
RPM : 50
Volume : 500 ml
Temperature : 37±0.5℃
Time : 20 hrs

The different formulations are made by varying the concentrations of the coating material. The core material is made up of the sugar spheres and this is coated by the core drug suspension which consists of the Active Pharmaceutical Ingredient along with the excipients like the mannitol, hydroxy propyl methyl cellulose, sodium lauryl sulphate, yellow oxide. Then this solution is coated unto the pellets. The sub coating material constituting of ethyl cellulose which is dissolved in isopropyl alcohol

is coated on the drug coated pellets. In the MSER F1 the ethyl cellulose coated was 2% and the dissolution profile for the MSER F1 pellets are observed. The results showed immediate drug release from the formulated pellets, that indicates that the retardant is very low in the MSER F1 formulation.

In the MSER F2 the coating material is increased to increase the retardant capacity of the pellets. The ethyl cellulose concentration was increased to 2.5%. Then these are evaluated for the dissolution test. the results reveled that the drug release in the first hour is much higher than the specified by the limits so this formulation is also discarded.

In the MSER F3, the product is formulated with more amount of the coating polymer to be coated on the core drug pellets. The polymer concentration was further increased to 3%. In this formulated pellets the dissolution profile showed better results compared to the old formulations which indicate that by increasing the quantity of the retardant or the polymer the drug release is delayed further. But these dissolution results does not comply with that of the limits specified in the first hour of the drug release, so this formulation is also discarded. then the next formulation is taken by further increasing the amount of the retardant.

In the MSER F4 the core pellets are coated with still more polymer compared to that of the MSER F3. In this the polymer concentration was increased to 3.5%. When these polymer coated pellets are evaluated for the dissolution profile, the results showed better drug release compared to that of the older formulations and also the drug release was in the limits specified for the drug release. But still the drug release does not comply with the Innovator drug release, so another formulation is made.

In MSER F5 the polymer concentration was further increased to 4% and the formulated pellets were evaluated for the drug release. The results showed a little

increase in the drug release but the dissolution results were not satisfactory and does not comply with the in house specifications. So another formulation was made by further increasing the concentration of the polymer.

In MSER F6 the polymer concentration was 4.5% and the dissolution results of these coated pellets showed a further more increase in the delay of the drug release but it was not satisfactory and does not comply with the in house specifications. But the results were nearer to the innovator drug release pattern.

In the MSER F7 the amount of the polymer is till increased to retard the drug release still further so that the drug release of the formulated drug complies with that of the Innovator drug release. The polymer concentration used in this formulation is 5%. After the formulation of the pellets the sample is taken and have been under gone for the dissolution studies. the results have shown very close drug release patterns when compared to that of the Innovator drug release pattern. but still further another formulation is taken by slightly increasing the polymer.

In MSER F8 the polymer content is still increased to further retard the dug release, the polymer content is only slightly increased. The polymer concentration was increased to 5.5%. Then after coating the samples are taken from the formulation and are evaluated for the drug release. The dissolution results showed more delayed drug release than the specified limits.

Table 33: Comparative dissolution profile for Metoprolol succinate prepared formulations MSER F1 to MSER F8.

S.No	Cumulative % drug release			
	1st hr	4th hr	8th hr	20th hr
MSER F1	48.5	72.3	92.4	99.8

MSER F2	41	69.83	86	98.67
MSER F3	36.5	57.67	83	98
MSER F4	29.4	52.6	79.4	97.9
MSER F5	26.83	47.5	76	97.83
MSER F6	21	37.67	69.167	98.167
MSER F7	13.83	33.67	56.67	97.33
MSER F8	8.67	27	47	94.5

Figure 17: Comparative dissolution profile for prepared formulations MSER F1 to MSER F8.

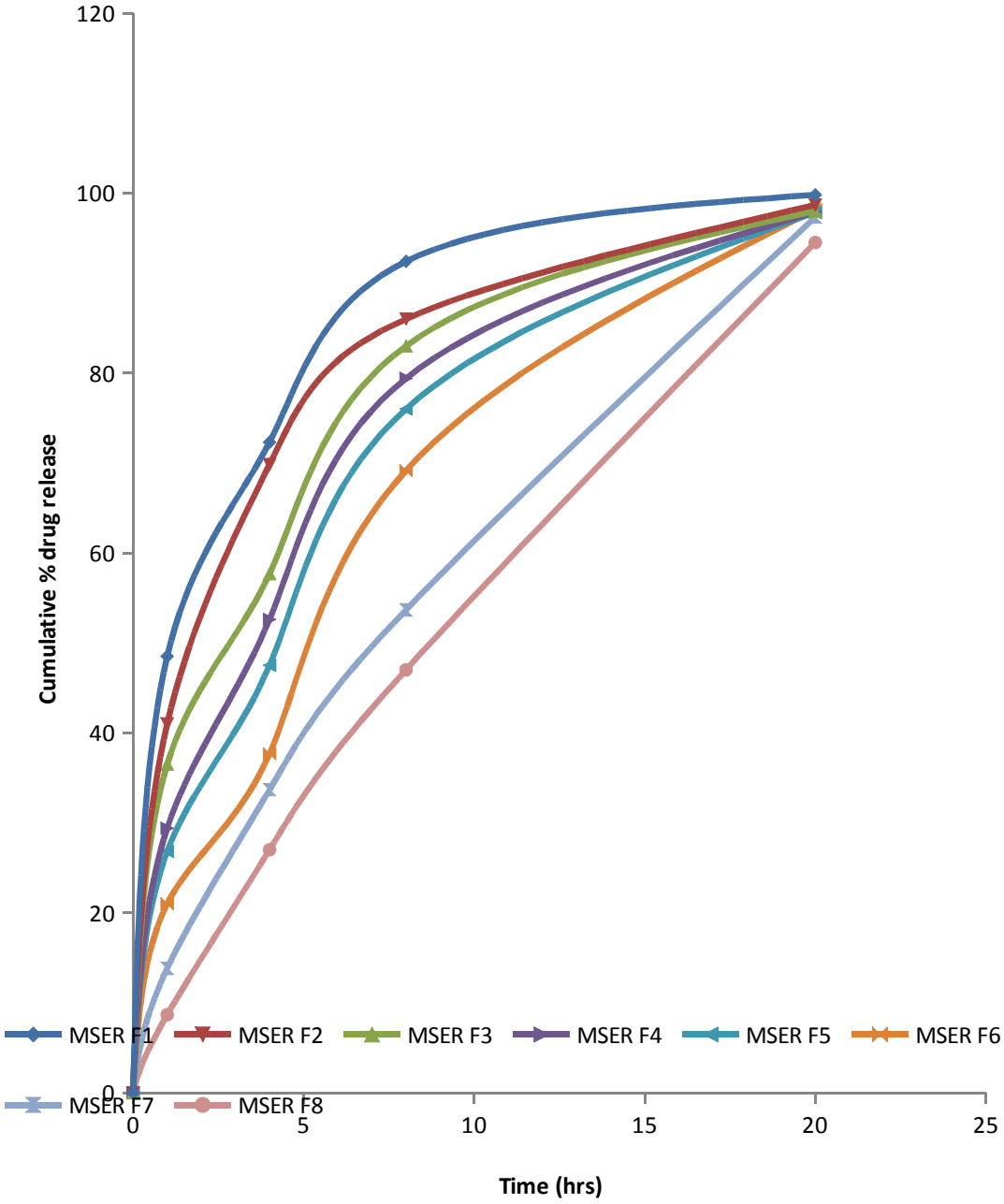
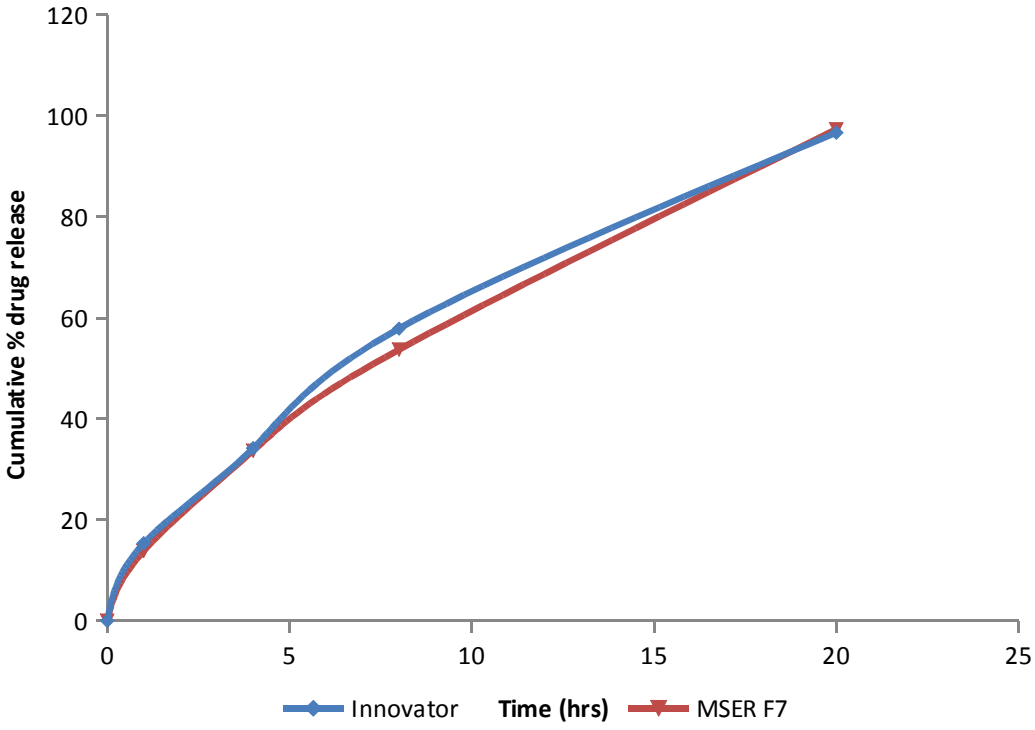


Table 34: Comparitive dissolution profile of MSER F7 and Innovator

S.No	Time (hrs)	Cumulative % drug release	
		Innovator	MSER F7
1	1	15.33	13.83
2	4	34.16	33.67
3	8	57.833	56.67
4	20	96.667	97.33

Figure 18: Comparative dissolution profile of MSER F7 and Innovator



When the drug release patterns of the different formulations and that of the Innovator are compared, it showed that the MSER F7 formulation complies better

with that of the Innovator drug release. So the MSER F7 pellets are optimized and the evaluation tests like the floe properties, compressibility properties, assay, and other evaluation tests are done.

After all the evaluation tests are done and by examining the results MSER F7 showed better results compared with all the other formulations, so the MSER F7 formulation is optimized and it also showed better dissolution results when compared with the innovator and complies with the innovator dissolution profile.

5.4 Characteristics of pellets for MSER F7 optimized batch.

Description

The prepared pellets are taken and they are examined visually for the the organoleptic characteristics and the pellets were found to be yellow in color, with spherical shape.

Hardness

Hardness of the pellets was found to be in the range of 6N to 8N and is given in the following table. It is determined by pharmatest hardness tester.

Table 35: Hardness of Metoprolol succinate pellets of different formulations.

Parameter	MSER F1	MSER F2	MSER F3	MSER F4	MSER F5	MSER F6	MSER F7	MSER F8
Hardness(N)	6	8	6	7	6	7	6	8

5.5 Loading of coated pellets and evaluation of capsules

The present study was undertaken to formulate and evaluate Metoprolol succinate extended release capsules. Formulation and processing development along

with evaluation of the capsules made with the optimized formulation. Results and discussion of the above studies are presented below. The optimized pellets equivalent to 25 mg of the metoprolol succinate drug is transferred into the pellets of 2 size. The average weight of the size 2 pellets is 64 mg.

Table 36: Compilations of capsules (mg/capsules)

S.No	Physical parameter	MSER F1	MSER F2	MSER F3	MSER F4	MSER F5	MSER F6	MSER F7	MSE R F8
1	MS(ER) pellets	25mg	25mg	25mg	25mg	25mg	25mg	25mg	25mg
2	Hard gelatin capsules (size 2)	1	1	1	1	1	1	1	1
3	Talc (mg)	1	1	1	1	1	1	1	1

5.6 Evaluation of capsules

Table 37: Evaluation of pellets loaded in capsules

S.No	Physical parameter	MSE R F1	MSE R F2	MSE R F3	MSE R F4	MSE R F5	MSE R F6	MSE R F7	MSE R F8
1	Weight variation (mg)	124	132	138	142	147	153	158	162
2	Assay % (99-101%)	100.36	99.84	99.25	99.68	99.89	99.45	99.78	99.68
3	Content uniformity %	100.6	100.2	100.9	99.6	99.7	99.5	100.8	100.6
4	Disintegration time	8min 45sec	9min 23sec	9min 45sec	9min 56sec	10min 12sec	10min 23sec	10min 45sec	10min 48sec

The evaluation studies for capsules loaded with the pellets have been carried out and the results have been given in the above table. By studying the above results it shows that the pellets are uniformly filled into the capsules. The assay results and

uniform content results reveal that the drug is uniformly coated into the pellets and each capsule contain equal amount of the drug in them. The disintegration tests also reveal that the capsules disintegrate immediately and releases the pellets into the gastro intestinal tract.

5.7 *In-vitro* Release kinetics

Data of *in vitro* drug release were fit into different equations and kinetic models to explain the release kinetics of Metoprolol succinate from the extended release pellet. The kinetic models used were a Zero-order equation, Higuchi's model and Peppa's models. The obtained results in these formulations were plotted in various model treatment are as follows. I.e. Cumulative percentage drug release Vs Square root of time (Higuchi's) and Log cumulative percentage release Vs Log time (Peppa's). To know the mechanism of drug release from extended release pellet, the drug release data was fit into Higuchi's models.

Mechanism of drug release

To find out the mechanism of drug release from hydrophilic pellets, the *in vitro* dissolution data of each formulation with different kinetic drug release equations. Namely Zero order: $Q=K_0t$; Higuchi's square rate at time: $Q=K_H$MSER $1^{/2}$ and Peppa's: $F=K_mt^n$, where Q is amount of drug release at time t, F is Fraction of drug release at time t, K_0 is zero order kinetic drug release constant, K_H is Higuchi's square root of time kinetic drug release constant, K_m is constant incorporating geometric and structural characteristic of tablet and n is the diffusion exponent indicative of the release mechanism. The correlation coefficient values (R) indicate the kinetic of drug release was zero order and the mechanism of drug release by Peppa's model indicates the non fickian evidenced with diffusion.

Table 38: *In-Vitro* Drug Release kinetics for MSER 7

S.No	*Zero order* data		Higuchi's data		Peppa's data	
	Time (hrs)	Cummulative % release	Square root of time	Cummulative % release	Log time	Log cummulative % release
1	0	0	0	0	0	0
2	1	13.83	1	13.83	0	1.140
3	4	33.67	2	33.67	0.602	1.527
4	8	56.67	2.83	56.67	0.903	1.753
5	20	96.667	4.47	96.667	1.301	1.985

Figure 19: Zero order plot of MSER F7

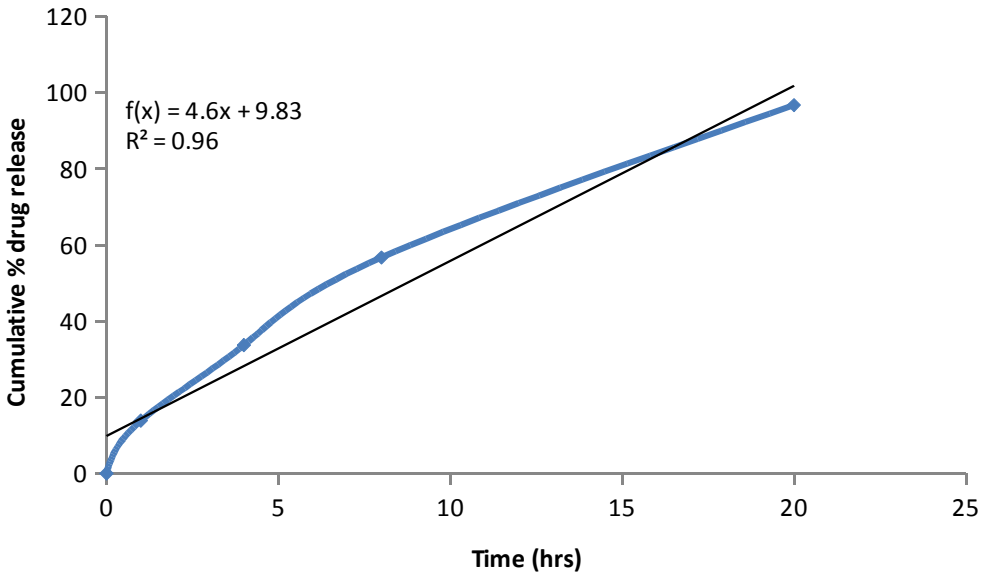


Figure 20: Higuchi's plot of MSER F7

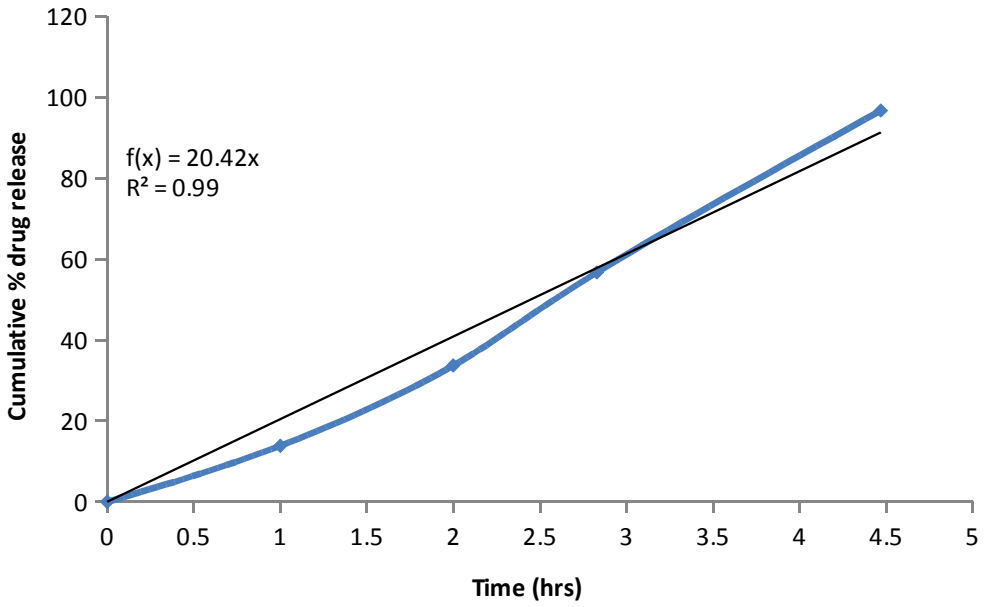
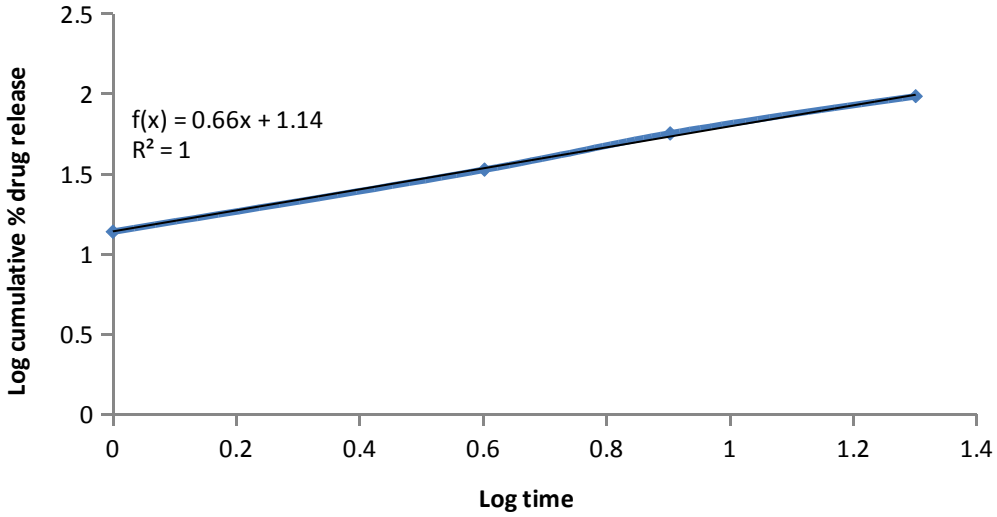


Figure 21: Peppa's plot of MSER F7



The In vitro release studies have been done and the results are incorporated into the zero order plot, Higuchi's plot and peppa's plot. All the plots showed that the drug release follows the zero order kinetics and thus the drug release from the dosage form is said to be of controlled drug release and it comes under the class extended release formulations.

5.8 Stability studies

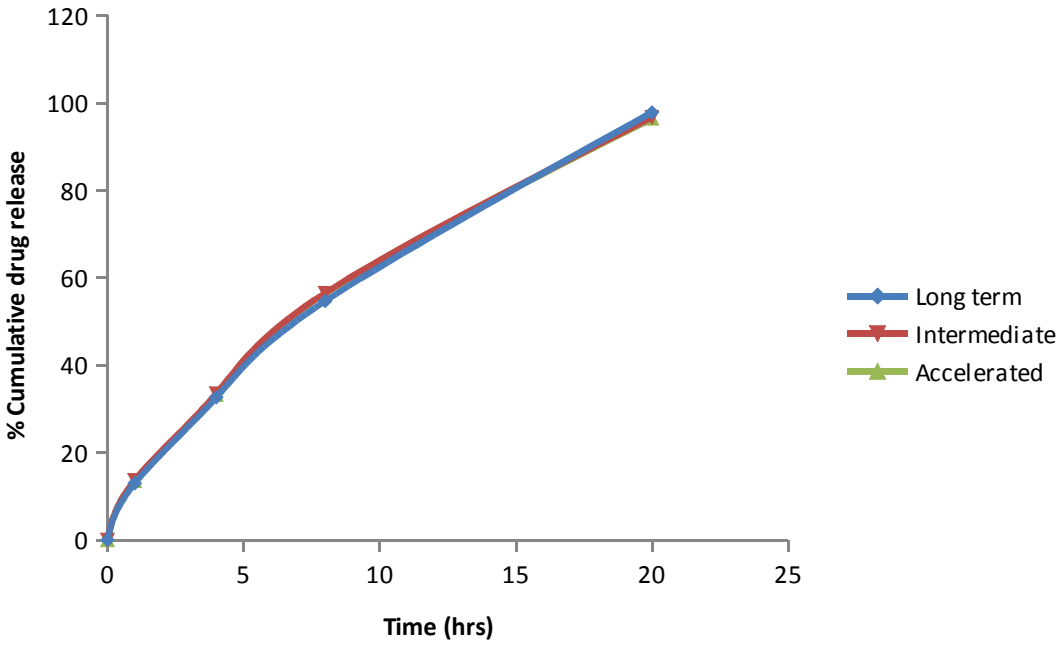
The stability studies were carried out according to ICH guidelines for optimized formulation i.e. MSER F7. The stability studies were carried out under 3 conditions i.e. Long term stability (25±2^{0}C/60% ±5% RH),Intermediate(30±2^{0}C/65% ±5%)and Accelerated stability studies (40±2^{0}C/75% ±5% RH). Then the pellets were stored under 3 conditions and the samples were withdrawn at every one month and evaluate the pellet parameters like description, assay and dissolution.

Sample were collected at an interval of 1, 2 and 3rd months and evaluated. Description, Assay and dissolution profile of MSER F7 stored at three conditions in 1M, 2M and 3M samples were found to be similar with that of initial samples and the results are given below.

Table 39: Physical evaluation of stability studies for optimized MSER F7 at different conditions carried out for 3 months duration.

Test	Month	Description	Assay
25^{0}C/60%RH (long term)	1	White to off white color	99.8
	2	White to off white color	99.67
	3	White to off white color	99.61
30^{0}C/ 65%RH (Intermediate)	1	White to off white color	98.45
	2	White to off white color	98.37
	3	White to off white color	97.91
40^{0}C/ 75%RH (Accelerated)	1	White to off white color	98.23
	2	White to off white color	98.05
	3	White to off white color	97.86

Test	Month	Cumulative % drug release (time in Hrs)			
		1	4	8	20
25^{0}C/60%RH (long term)	1	13.33	33.167	53.833	93.667
	2	13.83	33.67	56.67	97.33
	3	12.98	32.65	54.67	95.833
30^{0}C/ 65%RH (Intermediate)	1	13.75	33.59	56.59	97.13
	2	13.71	33.55	56.55	96.89
	3	13.65	33.48	56.51	96.73
40^{0}C/ 75%RH (Accelerated)	1	13.67	33.51	56.53	97.01
	2	13.61	33.44	56.49	96.75
	3	13.55	33.29	56.41	96.45



When significant changes does not occur at any time during 6 months testing at the accelerated storage conditions, additional testing at the intermediate storage condition should be conducted and evaluated tests for assay, content uniformity and dissolution studies.

6. SUMMARY AND CONCLUSION

- Metoprolol succinate is used in the treatment of hyper tension, angina pectoris (chest pain) and myocardial infarction. The study was undertaken with an aim to formulate Metoprolol succinate extended release pellets.
- Before going to develop the formulation a detail product literature review was carried out to know about the MUPS and type of dosage form available in market. The present study was focused to formulate extended release capsule by MUPS Technique.
- The drug excipient compatibility studies were also conducted and the results showed that there was no significant interaction between the drug and the excipients. The powder showed good solubility in water and also other solvents. The angle of repose of the powder was found to be 37.23°. The bulk density, tapped density, compressibility index and hausner's ration was found to be 0.375 gm/ml, 0.5727 gm/ml, 34.55 and 1.528 respectively. It showed poor flow properties.
- The different formulations were made mainly by using the different proportions of the excipients in both the primary and the secondary coating. The primary coating consists of the API, diluent, wetting agent and binder, and the secondary coating consists of the polymer coating.
- The sugar spheres were taken into the fluidized bed coater and the required amount of drug suspension (primary coating) was taken and coated unto them. The best trial was selected by conducting the evaluation tests. The results showed that as the concentration of the wetting agent (SLS) in decreased and

as the concentration of the binder (HPMC) is increased the pellets were formed satisfactorily and they also showed good flow properties.

- The optimized batch MSER CF7 is made up of 7% wetting agent and 4.5% binder. The evaluation tests that were conducted for the pellets also showed satisfactory results.
- These optimized drug coated pellets were taken for the secondary coating i.e. polymer coating. The polymer was coated in varied concentrations and the optimized formulation for polymer coating was identified.
- The formulation MSER F1 showed 48.5% drug release of the drug by the end of 1st hour. The formulation MSER F2 showed almost 70% drug release by the end of 4th hour. The formulation MSER F3, MSER F4 and MSER F5 showed drug release of 57.67, 52.6 and 47.5% of drug release by the end of 4th hour respectively. The drug release was further extended by increasing the concentration of the polymer. In the formulation MSER F6 the drug release was satisfactory but does not comply with that of the innovator drug release. The MSER F7 showed better results and the dissolution profile complies with that of the innovator drug release. It showed 97.33% of drug release in 20 hours. The MSER F8 showed still more further decrease in drug release, it showed only 8.67% of drug release in the 1st hour and 94.5% of drug release in 20 hours, so the formulation MSER F7 was optimized. The optimized coating consists of 5% of ethyl cellulose, 7.5% of Sodium lauryl sulphate and 4.5% of Hydroxy propyl methyl cellulose.
- The best trial was optimized by comparing the drug release profile with the innovator and the MSER F7 showed better results compared to the other formulations and the evaluation studies were conducted for the MSER F7. It

showed good results in formulation of stable dose.

- The pellets were evaluated for the flow properties, sieve analysis and accelerated stability studies for 3months. The pellets showed good flow properties and also showed uniform size which indicates uniform coating.
- The stability of the capsules and pellet was determined by conducting "Accelerated stability testing" in 40°C ± 2°C / 75% ± 5%RH and 25ºC ± 2 ºC/ 60% RH ± 5% RH conditions for 3 months as per ICH guidelines. Finally after the duration, the product was analyzed for assay, content uniformity and dissolution study. By the stability studies, the formulated metoprolol succinate extended release capsules and pellets proved to be stable throughout the period of the storage.
- The dissolution results after the long term (25^0C/60%RH), intermediate (300C/ 65%RH) and accelerated (400C/ 75%RH) were found to be equal to that of the optimized formulation (MSER F7).
- The In vitro drug release kinetic studies were conducted and the data was plotted for zero order, Higuchi's plot and pepp's plot and the graphs were plotted. The graphs showed that the drug release was of zero order. The mechanism of drug release was fount to be diffusion and dissolution and it indicates non fickian diffusion. The drug release was found to be of zero order.
- Extended release pellets have minimum volume in size, greater surface area and more surface activity. The area of the drug loaded pellets release rate was also more. And also there was no need of disintegration time for pellets in capsules. The risk of accumulation of the drug in the body is less. Drug release rate was more when compared with the innovator sample.

- Finally we concluded that the Metoprolol succinate pellets MSER F7 are prepared and these showed good physico-chemical properties and the dissolution results showed satisfactory results when compared with the innovator drug.

LIST OF FIGURES

LIST OF FIGURES

LIST OF TABLES

LIST OF TABLES

LIST OF TABLES

7. BIBLIOGRAPHY

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